Interim Clinical Outcomes in The Collaborative Initial Glaucoma Treatment Study Comparing Initial Treatment Randomized to Medications or Surgery

Paul R. Lichter, MD,[1] David C. Musch, PhD, MPH,[1,2] Brenda W. Gillespie, PhD,[3] Kenneth E. Guire, MS,[3] Nancy K. Janz, PhD,[4] Patricia A. Wren, PhD, MPH,[4] Richard P. Mills, MD,[5] and the CIGTS Study Group

Purpose: To report interim outcome data, using all available follow-up through 5 years after treatment initiation, in the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Design: Randomized clinical trial.

Participants: Six hundred seven newly diagnosed glaucoma patients.

Methods: In a randomized clinical trial, 607 patients with newly diagnosed open-angle glaucoma were initially treated with either medication or trabeculectomy (with or without 5-fluorouracil). After treatment onset and early follow-up, patients were evaluated clinically at 6-month intervals. In addition, quality of life telephone interviews were conducted at similar frequency to the clinical visits. Patients in both arms of CIGTS were treated aggressively in an effort to reduce intraocular pressure (IOP) to a level at or below a predetermined target pressure specific for each individual eye. Visual field (VF) scores were analyzed by time-specific comparisons and by repeated measures models.

Main Outcome Measures: VF loss was the primary outcome variable in CIGTS. Secondary outcomes of visual acuity (VA), IOP, and cataract were also studied.

Results: On the basis of completed follow-up through 4 years and partially completed through 5 years, VF loss did not differ significantly by initial treatment. Over the entire period of follow-up, surgical patients had a greater risk of substantial VA loss compared with medical patients. However, by 4 years after treatment, the average VA in the two groups was about equal. Over the course of follow-up, IOP in the medicine group has averaged 17 to 18 mmHg, whereas that in the surgery group averaged 14 to 15 mmHg. The rate of cataract requiring removal was greater in the surgically treated group.

Conclusions: Both initial medical or initial surgical therapy result in about the same VF outcome after up to 5 years of follow-up. VA loss was greater in the surgery group, but the differences between groups seem to be converging as follow-up continues. When aggressive treatment aimed at substantial reduction in IOP from baseline is used, loss of VF can be seen to be minimal in general. Because 4 to 5 years of follow-up in a chronic disease is not adequate to draw treatment conclusions, these interim CIGTS outcomes do not support altering current treatment approaches to open-angle glaucoma. *Ophthalmology 2001;108:1943–1953 © 2001 by the American Academy of Ophthalmology.*

Open-angle glaucoma is a leading cause of blindness[1]; yet, when detected and treated before its later stages, blindness is usually preventable.[2] To date, the approach to treatment aims to reduce the intraocular pressure (IOP) in hopes of reducing the progression of visual field (VF) loss. In measuring the effect of treatment, physicians are increasingly recognizing that the treatment approach, whether medical or surgical, can affect an individual patient's quality of life as can the disease itself.[3–7]

The Collaborative Initial Glaucoma Treatment Study (CIGTS) was undertaken to assess the effect on patients of two treatment approaches—initial therapy with topical medications or initial therapy with trabeculectomy—to newly

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[1] Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, The University of Michigan, Ann Arbor, Michigan.

[2] Department of Epidemiology, The University of Michigan, Ann Arbor, Michigan.

[3] Department of Biostatistics, The University of Michigan, Ann Arbor, Michigan.

[4] Department of Health Behavior and Health Education, The University of Michigan, Ann Arbor, Michigan.

[5] Department of Ophthalmology, University of Kentucky, Lexington, Kentucky.

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Reprint requests to Paul R. Lichter, MD, W. K. Kellogg Eye Center, University of Michigan, 1000 Wall Street, Ann Arbor, MI 48105.

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diagnosed open-angle glaucoma. Because the disease and its treatment affect the patient and not just the patient's eyes, the CIGTS protocol required that the same treatment approach would be used, if necessary, for both eyes of each patient. This approach also enables a valid comparison of the effects of these treatments on patients' quality of life. In a companion article,[7] the interim quality of life results are presented. This article presents clinical outcome data from the first 5 years of following CIGTS patients, including its primary outcome variable, VF change, as well as information on the secondary outcomes of visual acuity (VA), IOP, and cataract development. Future articles will discuss other results of the study.

Patients and Methods

Enrollment took place at 14 clinical centers from October 1993 through April 1997. Each clinical center and the study operations centers (administrative, coordinating, and quality of life) received institutional review board approval for the study. Eligible patients must have had (1) newly diagnosed open-angle glaucoma (primary, pseudoexfoliative, and pigmentary forms) in one or both eyes; (2) one of three combinations of qualifying IOP, VF changes, and optic disc findings; (3) a best-corrected VA of 20/40 or better in both eyes; (40) age between 25 and 75 years; (5) no prior ocular surgery (laser, refractive, conjunctival, or intraocular); (6) limited or no prior treatment (no more than 14 days of topical therapy and no such therapy for glaucoma for at least 3 weeks before the first baseline examination); (7) ability to meet the follow-up requirements for a minimum of 5 years; and (8) written informed consent. Consecutive cases of eligible patients were recruited at each clinical center.

Patients were randomly assigned using a form of adaptive randomization, termed minimization,[8] in which patients were assigned to the treatment group that resulted in optimal balance across five strata: age, 25 to 54, 55 to 64, 65 to 75; center (14 sites); gender (male, female); race (African American, white, Asian, other); and diagnosis (primary, pigmentary, and pseudoexfoliative forms of open-angle glaucoma). Once randomly assigned, patients in the surgical arm underwent trabeculectomy (with or without 5-fluorouracil at the surgeon's discretion) in their study eye within 14 days of random assignment. If further treatment was required, argon laser trabeculoplasty (ALT) 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, which usually began with a topical β-blocker, followed by an alternate single topical therapeutic agent, dual topical therapy, triple topical therapy, an alternate combination of triple topical therapy, and optional additional topical and/or oral medications. If further treatment was required, the next treatment step was ALT, followed by trabeculectomy (with or without 5-fluorouracil at the surgeon's discretion), medication, trabeculectomy with an antifibrotic agent, and medication.

Criteria for intervention failure had to be met each time that a further treatment step was initiated. A full description of these criteria are described in Musch et al.[9] Patients had to demonstrate consistently elevated IOP over a target pressure established at baseline or demonstrate consistently documented VF loss over the amount of VF loss present at baseline to qualify for further treatment steps. VF loss had to be documented on three consecutive tests performed at separate clinic visits. Target pressure was based on the patient's reference IOP (the mean of six separate IOP measurements taken in the course of the two baseline visits) and their reference VF score (the mean of VF scores from at least two Humphrey 24-2 VF tests taken during the two baseline visits). The target IOP was then calculated as follows: target IOP = [1 − (reference IOP + VF score)/100] × (reference IOP). Assessment of outcomes took place at the study's clinical centers, where standardized testing and examination were conducted by certified examiners at 3 and 6 months after treatment initiation and every 6 months thereafter. A full description of the study's organization, criteria for entry, treatment sequences, outcome assessment methods, follow-up procedures, and baseline characteristics of enrolled patients is provided in Musch et al.[9]

The primary study outcome was VF loss, which was measured at each follow-up visit using the Humphrey full threshold 24-2 testing strategy. VF scores were generated on the basis of a weighted summary of the deficits on the total probability plot. Increasing scores reflected increasing VF loss and ranged from 0 to 20. The VF score algorithm is described in Lichter et al.[10] An important CIGTS outcome, health-related quality of life and its relationship to clinical outcomes, is the focus of a companion article.[7] Secondary outcomes included change in best-corrected VA measured using the Early Treatment Diabetic Retinopathy Study protocol, change in IOP (measured by Goldmann tonometry), and the occurrence of cataract extraction. Sample size estimation was driven by the quality of life outcomes, which were anticipated to have greater variability than the clinical outcomes. Estimates of variability in these outcomes were derived from the literature and from pilot studies. Examples include a 4.0 unit difference in the Symptom Impact Score (standard deviation, 14.7 units), which would require 284 patients per group for 90% power, and a difference in the percentage of visual fields that demonstrate stability at 3 years of 20%, which would require 106 patients per group for 90% power. With allowance for censoring events (death, losses to follow-up, etc.), an enrollment goal of 300 patients per group was established.

Statistical analyses in this report include only data on the first eye treated for each patient. Treatment group comparisons followed the intent-to-treat principle. A descriptive evaluation of the pattern of change over time in VF and VA scores and IOP values between treatment groups was initially conducted without adjustment for any covariates. Time-specific comparisons of mean values were conducted using Student's t tests. Then, repeated measures analysis of variance[11] was used to investigate the effect of treatment on mean values of the outcomes through 5 years after random assignment. To investigate potential treatment effects on substantial VF and VA loss, substantial VF loss was defined as a 3 unit increase in VF score from baseline at any given follow-up time, and substantial VA loss was defined as a 3-line (15 letter) loss. Repeated measures logistic regression, using generalized estimating equations,[12] was used to assess treatment differences in rates of substantial loss over the available follow-up after random assignment. All repeated measures analyses adjusted for time on study (up to 5 years), stratification factors (diagnosis, age, race, gender), and baseline value. Center effects were evaluated in all models. They were not significant and were dropped from the models. To model the correlation between measurements on a person, a heterogeneous Toeplitz structure was used in the analysis of variance models, and a heterogeneous compound symmetry structure was used in the logistic models. The repeated measures analyses were performed using SAS Proc Mixed and SAS Proc Genmod.[13] Probability of cataract extraction over time was estimated by Kaplan-Meier analysis,[14] and treatment differences were tested with the log rank test,[15] both using SAS Proc Lifetest.[13]

Table 1. Demographics and Ophthalmic Status of Enrolled Patients by Treatment Group

Patient Characteristic	Medicine (n = 307)	Surgery (n = 300)	*P* Value*
Categorical variables	*N (%)*	*N (%)*	
Gender: female	143 (47%)	130 (43%)	0.47
Race: white	167 (54%)	170 (57%)	0.63
Immediate family history of glaucoma†	99 (32%)	102 (34%)	0.71
Hypertension	122 (40%)	103 (34%)	0.20
Diabetes	60 (20%)	42 (14%)	0.09
Smoking history: current	62 (20%)	65 (22%)	0.73
Glaucoma type: POAG	278 (91%)	272 (91%)	0.93
Quantitative variables	*Mean (SD)*	*Mean (SD)*	
Age, in years	56.9 (11.2)	58.1 (10.6)	0.19
Qualifying IOP: in mmHg	27.6 (5.5)	27.4 (5.7)	0.71
Reference VF score	4.6 (4.2)	5.0 (4.3)	0.15
VA score	85.6 (5.9)	85.8 (5.5)	0.62
Horizontal CDR	0.6 (0.2)	0.6 (0.2)	0.70
Vertical CDR	0.7 (0.2)	0.7 (0.2)	0.51

**P* values result from either Yates' corrected chi-square tests contrasting proportions or independent two-sided Student's *t* tests contrasting means in the medical and surgical groups.

†Immediate = parents, siblings, children.

CDR = Cup/disc ratio; IOP = intraocular pressure; N = number; POAG = primary open-angle glaucoma; SD = standard deviation; VA = visual acuity; VF = visual field.

Results

Fourteen clinical centers screened 1190 subjects for enrollment from October 1993 through April 1997. Of those screened, 728 (61%) were found to be eligible to participate. Six hundred seven (83%) of these eligible patients agreed to participate, and the remaining 121 (17%) decided against participation. The latter patients were older than those who agreed to participate. Reasons for refusal included concerns regarding surgery (n = 43, 36%), study burden (n = 28, 23%), lack of interest (n = 21, 17%), randomization (n = 15, 12%), and assorted other factors (n = 14, 12%).

Selected demographic and clinical characteristics of the study participants at enrollment are shown in Table 1. Most enrollees were diagnosed with primary open-angle glaucoma (550 of 607, 91%). CIGTS enrollees had an average age of 57.5 years (range, 28–75 years). Nonwhites made up 44% (270 of 607) of the group. Patients had an average IOP of 27 mmHg, a degree of VF damage that on average was mild (4.8 units on the VF scoring scale), and mild glaucomatous cupping of the optic disc (cup/disc ratios in the 0.6–0.7 range, on average).

Follow-up over time is displayed in Table 2. As of June 2001, information on follow-up status at 4 years after treatment initiation was available on all but six study patients, whose examinations had yet to be reported. Discounting deaths (n = 19 after 4 years of follow-up), study follow-up was ongoing for 91% (529 of 582) of patients 4 years after treatment initiation. One hundred sixty-one study participants have yet to reach their 5-year anniversary in the study. Therefore, the outcome data and results that follow are essentially complete through 4 years after treatment initiation; results for time intervals after 4 years are incomplete and subject to change. Protocol deviations were mostly minor (e.g., not performing a required repeat visual field in the timeframe dictated by the protocol). Three patients randomly assigned to surgery refused the intervention and were treated medically; two patients withdrew before treatment initiation because of major health events (one died, one had a cardiovascular event).

VF Results

An inspection of the mean VF scores over the 5 years since treatment initiation shows several trends (Fig 1). The surgically treated group had a mean VF score at baseline of 5.0 (standard deviation, 4.3). Five years after treatment initiation, this group's mean VF score is essentially unchanged, and throughout the available follow-up, very minimal change in the VF score is observed. The medically treated group had a baseline mean VF score of 4.6 (standard deviation, 4.2), which decreased to as low as 4.0 at years 1 and 2, but by 5 years after medical treatment initiation, increased to about the same level as the surgery group (5.0 VF units). Time-specific testing of intergroup differences shows significantly higher (i.e., worse) VF scores in the surgically treated group at 1 and 2 years after treatment initiation but no significant differences thereafter.

Given a somewhat lower mean VF score at baseline in the medically treated group, adjustment for this difference is appropriate to compare the two treatment groups' change over time. Table 3 (part A) displays the results of a repeated measures analysis of variance model, with adjustment for time on study, stratification factors (diagnosis, age, race, gender), and baseline VF value. The initial treatment approach had a marginally signif-

Table 2. Participant Availability for Follow-up at the Clinical Centers Over Time in the Collaborative Initial Glaucoma Treatment Study

Follow-up Status	Time after Treatment Initiation (in months)					
	Month 6	*1 Year*	*2 Years*	*3 Years*	*4 Years*	*5 Years*
Active*						
Surgery group (n = 300)	99.0% (297/300)	98.0% (294/300)	96.6% (284/294)	92.5% (270/292)	90.2% (257/285)	89.3% (183/205)
Medicine group (n = 307)	99.7% (306/307)	98.4% (301/306)	96.4% (293/304)	94.4% (285/302)	91.6% (272/297)	93.1% (201/216)
Overall	99.3% (603/607)	98.2% (595/606)	96.5% (577/598)	93.4% (555/594)	90.9% (529/582)	91.2% (384/421)
Inactive†	n = 4	n = 11	n = 21	n = 39	n = 53	n = 37
Died†	n = 0	n = 1	n = 9	n = 13	n = 19	n = 25
Follow-up interval yet to occur	n = 0	n = 0	n = 0	n = 0	n = 6	n = 161

*At each time point, the percentage who are active is calculated as the number active divided by the number of active and inactive patients. Deaths and follow-up not yet occurred are excluded.

†The numbers of patients who have died are cumulative across time. An inactive patient is defined as one for whom no visits have occurred beyond the stated follow-up time.

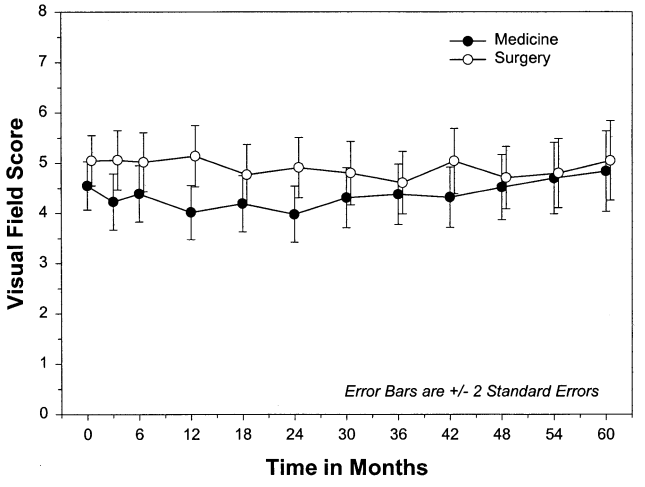

Figure 1. Collaborative Initial Glaucoma Treatment Study visual field score by time and treatment group.

icant effect on mean VF scores over time. The surgical group showed mean VF scores that were 0.36 units higher on average than the medical group ($P = 0.03$). Because a secondary outcome, cataract, influenced the VF score in a substantial manner (those with cataract had on average a 3.6 units greater VF score than those without cataract), a second model was constructed that incorporated an adjustment for cataract. The adjustment incorporated an indicator for VF data from visits within 12 months of cataract extraction as a covariate in the model. With this adjustment, the treatment effect was reduced to 0.28 units and was marginally significant ($P = 0.07$). No significant treatment by time interaction was seen.

Several other factors had an independent impact on the mean VF score. Those with higher VF scores at baseline, older patients, nonwhite patients, and diabetic patients showed higher VF scores over follow-up. Nonwhite patients had higher VF scores than white patients by an average of 0.34 units, and a 10-year increase in age increased VF scores by an average of 0.40 units. Diabetic patients had higher VF scores during follow-up than nondiabetic patients by an average of 0.71 units. A 1-unit increase in the baseline VF score was predictive of a 0.74 units increase in the follow-up VF scores. Nonlinearity of the baseline VF score effect was accounted for by adding the (baseline VF score) squared term to the model. All of these associations remained significant on adjustment for cataract.

A complementary analysis, using repeated measures logistic regression, addressed the proportion of patients at each follow-up interval who experienced clinically substantial VF loss (an increase in VF score from baseline of 3 or more VF score units). With data from 5691 patient visits after treatment initiation, a clinically substantial VF loss was observed at some point during 5 years of follow-up in 10.7% (314 of 2930) of medically treated and 13.5% (372 of 2761) of surgically treated patients' visits. Figure 2 shows the frequencies of substantial VF loss over time in each

Table 3. Repeated Measures Modeling Results for Visual Field Score

A. Analysis of Mean Scores (Repeated Measures Analysis of Variance)

Variable	Beta (Standard Error)	*P* Value	Direction of Effect
Treatment*	0.36 (0.16)	0.0310	Surgery ⇒ ↑ VF score
Baseline VF score (VF0)	0.74 (0.07)	0.0001	↑ VF0 ⇒ ↑ VF score
$(VF0)^2$	0.01 (0.01)	0.0238	See text
Age	0.04 (0.01)	0.0001	↑ Age ⇒ ↑ VF score
Sex	0.23 (0.17)	0.1678	No significant effect
Race	0.34 (0.19)	0.0690	Nonwhites ⇒ ↑ VF score
Diagnosis	0.38 (0.26)	0.1409	No significant effect
Diabetes	0.71 (0.22)	0.0016	Diabetes ⇒ ↑ VF score
Time	†	0.4084	No significant effect

*With adjustment for cataract, the treatment effect is marginally significant [beta (SE) = 0.28 (0.16), $P = 0.0787$].

†Not provided, due to multiple, time-specific values.

B. Analysis of VF Loss ≥3 Units from Baseline (Repeated Measures Logistic Regression)

Variable	Odds Ratio (95% Confidence Interval)	*P* Value	Direction of Effect
Treatment*	1.36 (0.99, 1.85)	0.0545	Surgery ⇒ ↑ VF score
Baseline VF score	1.02 (0.99, 1.06)	0.2349	↑ VF0 ⇒ ↑ VF score
Age	1.04 (1.02, 1.05)	<0.0001	↑ Age ⇒ ↑ VF loss
Sex	1.15 (0.85, 1.55)	0.3603	No significant effect
Race	1.50 (1.08, 2.07)	0.0145	Nonwhites ⇒ ↑ VF loss
Diagnosis	1.06 (0.59, 1.92)	0.8419	No significant effect
Diabetes	1.59 (1.07, 2.38)	0.0233	Diabetes ⇒ ↑ VF score
Time	1.01 (1.01, 1.02)	<0.0001	↑ Time ⇒ ↑ VF loss

*The treatment odds ratio is for surgery vs. medicine. With adjustment for cataract, the treatment effect remains marginally significant (odds ratio = 1.33, [95% confidence interval, 0.97, 1.82]; $P = 0.0746$).

VF = visual field.

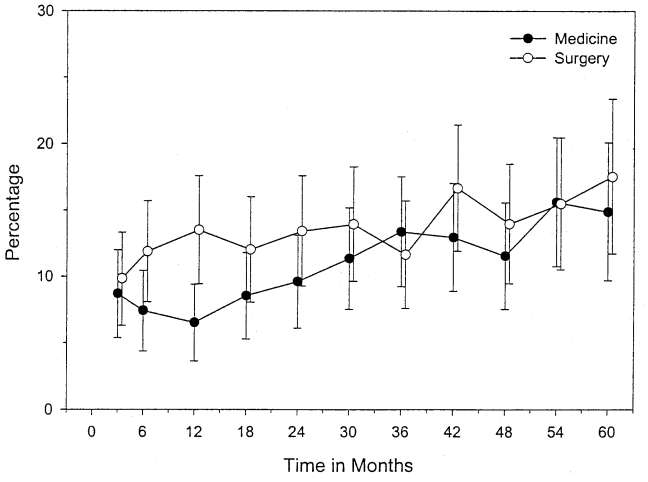

Figure 2. Percentage showing at least a 3 unit increase in Collaborative Initial Glaucoma Treatment Study visual field score by month of visit and treatment group.

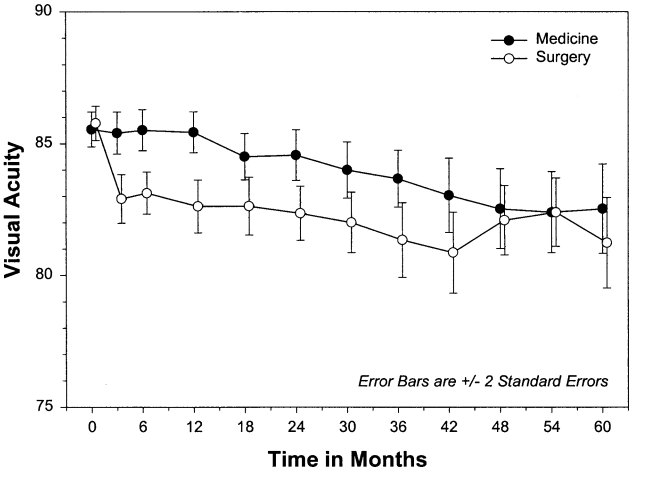

Figure 3. Visual acuity by time and treatment group.

treatment group. At most time periods, rates of substantial VF loss were somewhat higher in the surgery group, with the exception of months 3, 36, and 60, where rates were about equal or slightly greater in the medical treatment group. No significant treatment by time interaction was seen.

The logistic regression analysis revealed significant associations of a 3 unit or more VF score increase with age, race, history of diabetes, and time in study (Table 3, part B). Older age was associated with an increasing frequency of substantial VF loss (every 10-year increment in age increased the risk of VF loss by 40%). Nonwhites had a 50% increased risk relative to whites (adjusted odds ratio [OR], 1.50; 95% confidence interval [CI], 1.08, 2.07). Diabetic patients had a 59% increased risk relative to nondiabetic patients (adjusted OR, 1.59; 95% CI, 1.07, 2.38). The likelihood of substantial VF loss increased with time on study. Initial surgery had a marginally significant positive association with the risk of substantial VF loss (adjusted OR, 1.36; 95% CI, 0.99, 1.85) that remained about the same on adjustment for cataract. In a model that included adjustment for cataract, patients with cataract were at an increased risk of clinically substantial VF loss (adjusted OR, 4.71; 95% CI, 3.34, 6.65). The direction and significance of all other associations were unchanged on adjustment for cataract.

VA Results

On average, surgery resulted in a 3-letter loss of VA (about ½ line) evident at month 3 and beyond, whereas VA in the medicine group showed essentially no change during the first year of treatment. After the first year of follow-up, average VA decreased in both surgery and medicine groups (Fig 3). By 4 years after treatment initiation and thereafter, however, the average VA in the two groups was approximately equal. Time-specific comparisons of average VA show significantly better VA in the medicine group at all time points through 3.5 years after treatment initiation but no significant differences thereafter.

Repeated measures analysis of variance was performed to evaluate factors that influenced VA over time, with adjustment for time on study, stratification factors (diagnosis, age, race, gender), and baseline VA value. The initial treatment approach had a significant effect on mean VA scores over time (Table 4, part A). Patients undergoing medical treatment had slightly higher mean VA, by an average of 2.3 letters (about ½ line), than patients who received surgical treatment ($P = 0.0001$). Because a secondary outcome, cataract, influenced the VA score in a substantial manner (see later), adjustment for cataract was performed as described previously. The initial treatment effect remained significant in this model ($P = 0.0001$). No significant treatment by time interaction was seen.

As with VF scores, the baseline VA and its square were positively associated with VA over time. Patients with better VA at baseline tended to have better VA as follow-up progressed. Nonlinearity of the baseline VA effect was accounted for by adding the square of the baseline VA score to the model. White patients had higher VA on average than nonwhite patients by about 1 letter. Older patients had lower follow-up VA on average. Each 10-year increase in age was associated with a 1.4-letter decrease in VA score. Cataract (defined as visits within 12 months of cataract extraction) influenced the VA score in a substantial manner. Those with cataract, as defined previously, had on average a 14.8-letter lower VA score than those without cataract.

By use of repeated measures logistic regression, we addressed the proportion of patients at each follow-up interval who experienced clinically substantial VA loss (defined by us as 15 letters or more decrease in VA from baseline). A clinically substantial VA loss was observed at some point during 5 years of follow-up in 3.9% (115 of 2933) of medically treated patients' visits and 7.2% (200 of 2771) of surgically treated patients' visits. Figure 4 shows the frequencies of substantial VA loss over time in each treatment group. At all follow-up intervals though month 42, rates of substantial VA loss were higher in the surgery group. From month 48 on, with incomplete follow-up, rates of substantial VA loss are either about equal (months 48 and 54) or slightly greater (month 60) in the surgical treatment group. No significant treatment by time interaction was seen.

The logistic analysis (Table 4, part B) revealed significant associations with a 15-letter or more VA decrease for treatment, age, race, history of diabetes, and time on study. Surgery group patients were twice as likely to have a clinically substantial VA loss than medical group patients (adjusted OR, 2.01; 95% CI, 1.32, 3.06). Older patients were more likely to experience a clinically substantial VA loss; the likelihood increased 40% for every 10-year increment. Nonwhites were at a marginally increased risk relative to whites (adjusted OR, 1.52; 95% CI, 0.98, 2.37). Diabetic patients were at a higher risk of substantial VA loss than nondiabetic patients (adjusted OR, 2.23; 95% CI, 1.37, 3.63). VA loss increased with increasing time on study. As expected, patients

Table 4. Repeated Measures Modeling Results for Visual Acuity
A. Analysis of Mean Scores (Repeated Measures Analysis of Variance)

Variable	Beta (SE)	*P* Value	Direction of Effect
Treatment*	2.32 (0.42)	0.0001	Surgery ⇒ ↓VA
Baseline VA score (VA0)	4.07 (0.88)	0.0001	↑VA0 ⇒ ↑VA
$(VA0)^2$	−0.02 (0.01)	0.0001	See text
Age	−0.14 (0.02)	0.0001	↑ Age ⇒ ↓VA
Sex	0.65 (0.43)	0.1290	No effect
Race	0.97 (0.46)	0.0337	Nonwhites ⇒ ↓VA
Diagnosis	−0.66 (0.70)	0.3474	No effect
Diabetes	0.89 (0.60)	0.1430	No effect
Time	†	0.0001	↑Time ⇒ ↑VA loss

*With adjustment for cataract, the treatment effect remains significant [beta (SE) = 2.10 (0.41), P = 0.0001].

†Not provided, due to multiple, time-specific values.

with cataract were at an increased risk of clinically substantial VA loss (adjusted OR, 18.61; 95% CI, 11.98, 28.89). However, adjustment for the effect of cataract did not influence the significance of other factors, including initial treatment approach, on the VA outcome.

IOP Results

Although both medicine and surgery decreased IOP significantly after treatment initiation (Fig 5), the amount of decrease was greater in the surgery group, and the difference between treatment groups was maintained over 5 years of observation. Those receiving initial surgery had a baseline IOP average of 27 mmHg that decreased after surgery to the 14 to 15 mmHg range through 5 years. The medically treated group's average baseline IOP of 28 mmHg decreased after medication to the 17 to 18 mmHg range during follow-up. Time-specific comparisons of IOP between groups show statistically significant differences at all time points. Therefore, IOP reduction in the medically treated patients, although substantial, was less than that seen in the surgical group.

Repeated measures modeling of the factors associated with IOP over time showed significant effects of treatment. Consistent with the information displayed in Figure 5, the surgery group's average IOP over time, adjusted for other factors, was 3.0 mmHg lower than the medicine group's IOP ($P = 0.0001$). Other factors that significantly influenced IOP over time included baseline IOP and its square (higher baseline IOP, higher follow-up IOP; $P = 0.0001$), race (the average IOP in whites was 0.7 mmHg lower than in nonwhites; $P = 0.02$), time on study ($P = 0.0001$), and a treatment by time interaction (the pattern of IOP across time is flat in the medicine group, and shows a slight increase across time in the surgery group; $P = 0.0001$).

Cataract Extraction Results

Initial surgical treatment resulted in the development of more cataracts requiring removal than initial medical treatment. The crude proportion of cataract extraction in the surgery group (52 of 300; 17.3%), unadjusted for variable follow-up, was almost three times greater than the proportion in the medicine group (19 of 307; 6.2%). The Kaplan-Meier estimates (Fig 6) demonstrate the intergroup difference. By 3 years after treatment initiation, the survival curves show an extraction probability of 11.6% (standard error, 1.9%) in the surgical group versus 2.7% (standard error, 1.0%) in the medical group. The surgery group's higher cataract extraction probability over time significantly exceeds that of the medicine group ($P = 0.0001$, log rank test).

Treatment Crossover

The frequency of treatment crossover in the medical group (from treatment with medicine to trabeculectomy) and surgical group (from trabeculectomy to medical treatment) was comparable (medical group, 8.5%; surgical group, 8.3%; $P = 0.80$, log rank test). Although ALT was not viewed as an intervention with crossover implications, its earlier use in the medical group than in the surgery group resulted in a significant difference in the time to ALT comparison ($P = 0.03$, log rank test). By 1 year after treatment

B. Analysis of VA Loss ≥15 Letters from Baseline (Repeated Measures Logistic Regression)

Variable	Odds Ratio (95% Confidence Interval)	*P* Value	Direction of Effect
Treatment*	2.01 (1.32, 3.06)	0.0011	Surgery ⇒ ↑VA loss
Baseline VA score (VA0)	†	0.0020	↑VA0 ⇒ ↑VA
$(VA0)^2$	†	0.0020	See text
Age	1.04 (1.02, 1.07)	<0.0001	↑Age ⇒ ↑VA loss
Sex	1.26 (0.85, 1.87)	0.2527	No Effect
Race	1.52 (0.98, 2.37)	0.0627	Nonwhites ⇒ ↑VA loss
Diagnosis	1.28 (0.64, 2.57)	0.4855	No effect
Diabetes	2.23 (1.37, 3.63)	0.0012	Diabetes ⇒ ↑VA loss
Time	1.02 (1.02, 1.03)	<0.0001	↑Time ⇒ ↑VA loss

VA = visual acuity.

*With adjustment for cataract, the treatment effect remains significant (odds ratio, 2.13; 95% confidence interval [1.39, 3.25]; $P = 0.0005$).

†Not reported because of complexity of interpreting odds ratios in the quadratic relationship of baseline VA score with VA loss.

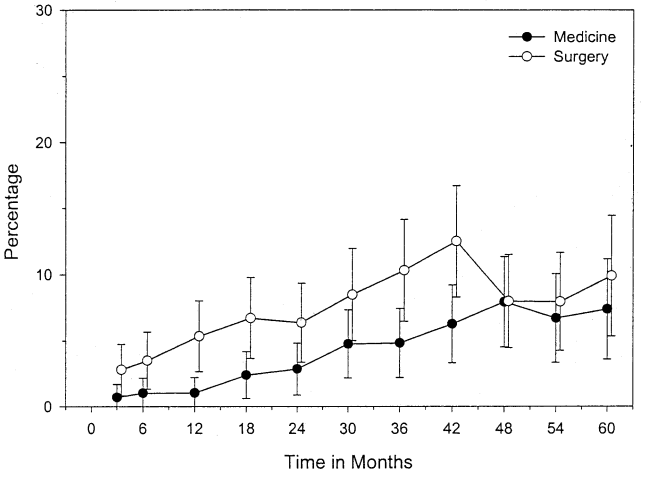

Figure 4. Percentage showing at least a 15-letter visual acuity loss by month of visit and treatment group.

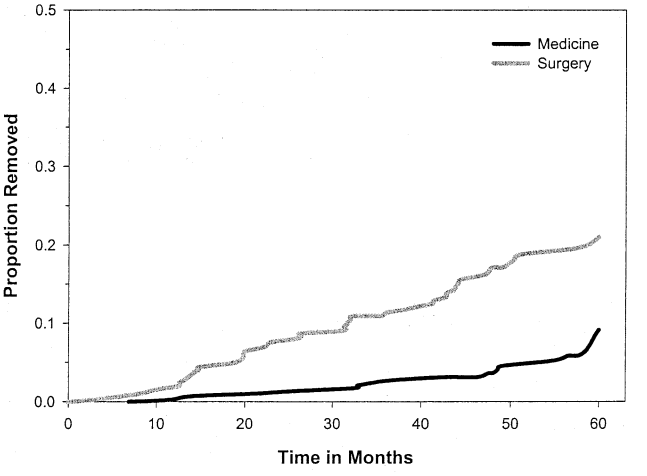

Figure 6. Kaplan-Meier estimates of the probability of cataract removal by time since randomization for each treatment group.

initiation, Kaplan-Meier survival curve estimates show 23.6% of medicine group patients undergoing ALT versus 11.8% of surgery group patients. By 4 years, the two groups' ALT rates have converged but still differ by treatment group (medicine, 27.9%; surgery, 20.8%).

Surgical Complications

Intraoperative complications of trabeculectomy were evaluated in all surgeries (n = 525) performed in the CIGTS (the total includes fellow eye surgeries). The most frequent surgical complications included intraoperative bleeding in the anterior chamber (n = 37, 7.1%) and buttonhole (n = 5, 1.0%). Expulsive choroidal hemorrhage did not occur. During the first postoperative month, with information available on 517 surgeries, the most frequent complications noted were a shallow or flat anterior chamber (n = 73, 14.2%), encapsulated bleb (n = 61, 11.9%), ptosis (n = 61, 11.9%), serous choroidal detachment (n = 58, 11.3%), and anterior chamber bleeding or hyphema (n = 54, 10.5%). The CIGTS Data and Safety Monitoring Committee has not identified safety issues of concern.

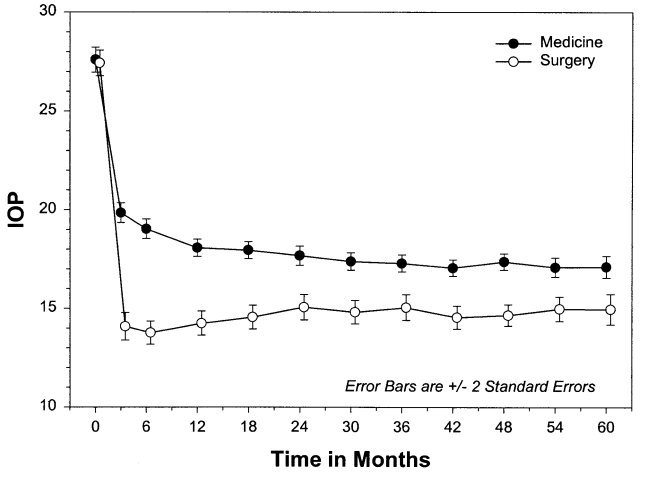

Figure 5. Intraocular pressure by time and treatment group.

Discussion

When the CIGTS was organized, studies in England and Scotland[16,17] suggested that early trabeculectomy was preferable to treatment with medication to prevent progression of VF loss. The authors attributed differences in VF progression to the extent of IOP control, which was best in the surgery group. It seems that the patients in the British studies may have had more advanced glaucoma than did our patients, which could account for greater visual field progression in a shorter period of time than our study has shown. In addition, our study treated patients in the medical group particularly aggressively to achieve an individually calculated target pressure. New medications, not available at the time of the British studies, may have contributed to a somewhat greater reduction in IOP than achieved in the British studies.

Although these interim follow-up results show a clear and sustained difference in the IOP between the medical and surgical groups, both groups had a substantial reduction in IOP from baseline values of 28 mmHg and 27 mmHg, respectively. The surgical group's mean IOP after treatment has been in the 14 to 15 mmHg range compared with a 17 to 18 mmHg IOP range for the medical group. This represents a mean percent reduction in IOP of approximately 48% in the surgical group and approximately 35% in the medical group. On the basis of increasing evidence presented in the literature,[18–25] one would expect the group with the lower IOP to have less VF loss over time than the group with the higher IOP. Yet, in CIGTS, there is not yet that difference. In fact, in all analyses, the medical group had slightly better VF scores than did the surgery group.

One explanation for this result may be that the two groups were both treated aggressively in terms of IOP reduction. The CIGTS protocol sets a target IOP as a treatment goal. The treating physician then increases treatment until the target IOP is reached or until maximum tolerated treatment has been prescribed without crossing to the opposite treatment (i.e., from medicine to trabeculectomy or from trabeculectomy to medicine). At that point

treatment is maintained unless a protocol-established tolerance IOP is exceeded and/or VF loss occurs, at which point an intervention failure permits the next step in the treatment protocol. This aggressive treatment approach for each group has resulted in mean IOPs in each group that are less than the 18 mmHg level that the Advanced Glaucoma Intervention Study[25] used as a reference point to assess the effect of IOP on VF loss. Results of that study showed that VF loss was reduced substantially if IOP was maintained at less than 18 mmHg.

Intuitively, this means that if a lower IOP—even a little bit lower—is better in terms of slowing or preventing progression of VF loss, then because both groups have had such substantial IOP reduction from baseline, it will take more time than the length of the current follow-up to determine differences in VF loss between the two groups. More time will show whether this trend continues and whether the IOP difference between the groups is sustained. It was noted in our results that, although the IOP curve in the medicine group is flat, the surgery group's IOP curve is trending slightly higher.

Another possible protocol-related factor to consider in evaluating these findings is the fact that patients in both treatment groups were given the next treatment step if a protocol-established tolerance IOP is exceeded and/or VF loss occurs. If the rate or timing of administering further treatment varied between treatment groups, this factor may have influenced the outcomes. However, the frequency of treatment crossover in the medical group (from treatment with medicine to trabeculectomy) and surgical group (from trabeculectomy to medical treatment) was comparable. Differing crossover timing or rates between initial treatment groups, then, cannot be used as a means to explain outcomes that differ between the two treatment groups. The rate of ALT (i.e., a move to the second treatment step in both groups) was higher in the medically treated group compared with the surgery group. This most likely reflects the fact that the medically treated group had higher mean IOPs, and more of these patients would likely fail to meet IOP target/tolerance IOPs than patients in the surgery group, whose mean IOP was lower.

It seems that cataract development played a role in the intergroup VF difference that was found in analyzing the mean VF scores over time. On adjustment for cataract, the significance of treatment in the model, albeit not overly strong ($P = 0.03$), diminished to a marginally significant level ($P = 0.07$). It is well known that cataract can, on its own and entirely independent of glaucomatous damage, alter VF results, so that the amount of loss measured on the VF is exaggerated.[26–30] Therefore, although initial surgical treatment led to an increased need for lens removal relative to the initial medicine group, this effect also contributed to an increase in VF loss within the surgical group.

Cataract extraction was an earlier and more frequent occurrence within those randomly assigned to initial surgery. With adjustment for censoring, after 5 years of follow-up the probability of cataract extraction approached 20% within the surgery group, which is about twice the rate observed in the medicine group. Although cataract extraction is a highly successful procedure that almost always restores a patient's vision, the increased rate of cataract extraction in the surgery group needs to be considered in the context of future treatment recommendations that arise from this study. The impact of cataract and its surgical correction on our patients' health-related quality of life will be part of a future study article.

We found that VF scores over time after treatment initiation were significantly higher in older patients, in nonwhite patients, and in diabetic patients. Interestingly, when the Advanced Glaucoma Intervention Study Investigators reported on the effect of cataract on their findings, they found that the higher VF scores in African Americans remained significant after correction for cataract.[30] There are likely multiple underlying reasons for the fact that being older or being a nonwhite (which in our study meant being an African American in most cases) places one at an increased risk of more VF loss at diagnosis and progressive loss after treatment. Although older age and African American race have been consistently associated with a higher risk of glaucoma, Fraser et al[31] found that an African Caribbean patient is more than four times as likely to initially be seen with advanced VF loss than a white patient. These authors also noted that older age was significantly associated with advanced field loss at presentation. On the basis of observations that African Americans are at higher risk of blindness caused by glaucoma,[32–34] some have suggested that open-angle glaucoma may be a more severe disease among African Americans. Few studies, however, have had the opportunity to associate age and race with progression in field loss after diagnosis and initiation of treatment. In the CIGTS, nonwhites had statistically higher IOP levels over follow-up. Because IOP control has been identified as an important factor in preventing VF loss,[25] it may be that poorer IOP control in African Americans underlies their higher risk of advancing VF loss during treatment. Diabetic patients have been reported to have higher IOP and cup/disc ratios than nondiabetic patients,[35] which may account for the increased risk of progressive VF loss we observed. This finding deserves further evaluation.

The VA results revealed an initial decrease in VA in the surgery group that was not observed in the medicine group and resulted in lower mean VA in the surgery group that persisted through 3.5 years after surgery. After that time, mean acuity levels were comparable in the two treatment groups up to 5 years of follow-up (Fig 3). Patients in the surgery group were at greater risk to have a significant loss of acuity at some point during the follow-up period (Fig 4). The role of cataract development and extraction in these trends is certainly important to consider and may be a key factor in the convergence of VA in the two groups that occurred from 4 years on. Nonwhites, older patients, and those in the study a longer time were found to be at greater risk for significant VA loss. Adjusting for the presence of cataract did not influence the significance of these other factors. This finding differs from the Advanced Glaucoma Intervention Study outcomes, wherein the presence of cataract had an even greater influence on VA than it did on VF.[30] Perhaps our method of measuring cataract presence was not specific enough to adjust for all of the effects of cataract on VA.

Our outcome analyses rely on clinical findings from the

primary study eye, which is the first eye to receive treatment in the protocol. The protocol specified mandatory treatment criteria for eyes, and so treatment of the fellow eye at times was delayed long after treatment of the study eye, and for some patients treatment of the fellow eye has yet to be undertaken. As of early 2001, 33% (200 of 607) of fellow eyes remained untreated. Therefore, for clinical outcomes, the primary study eye's results are most pertinent. The companion article[7] assesses patients' answers to questions about health perceptions and includes, of course, any symptoms related to both eyes. Although the clinical outcome variables are important, so too are health-related quality-of-life outcome variables. Because it is fortunate that most patients appropriately treated for their glaucoma will not become blind,[2] it may be even more important to know which of two treatments that will prevent blindness is better in terms of a quality-of-life perception on the part of patients than to know whether one or the other of those treatments results in slightly more or less—albeit statistically and even clinically significant—VF or VA loss.

As CIGTS patients are followed over the course of their disease, we will be able to assess whether there is any important difference resulting from how these patients were treated at the outset of the study. It is evident from our interim outcomes that patients in both the initial medication and the initial surgery groups had their IOP lowered significantly and that, at least in these first few years, most patients did not experience substantial loss of visual function (VF or VA).

Thus far, the data presented in this first CIGTS clinical outcomes article and in our companion quality-of-life outcomes article[7] do not suggest a change in the way ophthalmologists currently manage their patients with newly diagnosed open-angle glaucoma. Given the chronic nature of glaucoma, outcome data from longer term follow-up will be required to form the basis for specific treatment recommendations. The CIGTS remains an ongoing clinical trial in which the patients continue to be managed according to study protocol.

Appendix

The CIGTS Study Group by Center

Clinical Centers

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

California. Doheny Eye Institute, University of Southern California, Los Angeles, California: Rohit Varma, MD (PI, 1997–present); Dale K. Heuer, MD (PI, 1993–1997); Brian A. Frances, MD (CI); Donald S. Minckler, MD (CI); A. Frances Walonker, CO, COMT (CC); Tracy Nichols, CRA, COA (OP); Danny Romo (T).

Florida. Department of Ophthalmology, University of Florida, Gainesville, Florida: Mark B. Sherwood, MD (PI); J. William Doyle, MD (CI); M. Fran Smith, MD (CI); Revonda M. Burke, COMT (CC); Kay Barker (OP); Donna McDavid, COMT (T); Renae Preston, LPN, COMT (T); Diana Shamis, MHSE, CO, COMT (T).

Maryland. Wilmer Ophthalmologic Institute, Johns Hopkins University, Baltimore, Maryland: Henry D. Jampel, MD (PI); Harry Quigley, MD (CI); Donald J. Zack, MD, PhD (CI); Rachel Scott, BS, COA (CC); Dennis Cain (OP); David Emmert (OP); Therese Fila, COT (T); Rhonda Miller, COA (T); Siobhan E. Sheehan (T); James G. Sutton, Jr. (T); Lula West, COA (T).

Minnesota. Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota: Martha M. Wright, MD (PI); Emmett F. Carpel, MD (CI); Sally Cook, BA (CC); Ann Holleschau, BA (Asst. CC); Sabrina Rolfer, COT (T); Pat Stanaitis, CRA (OP); Terry M. Takara, BS (T); Daniel Venezia, CRA (OP).

New York. Glaucoma Consultants of the Capital Region, Albany, New York: Steven T. Simmons, MD (PI); Kathy Caswell, RN (CC); Penny Adamec (T); Sherri Ferriero (T); Joe Fisher (OP).

Ophthalmic Consultants of Long Island, Lynbrook, New York: Stanley J. Berke, MD (PI); Richard T. Sturm, MD (CI); Ronald M. Caronia, MD (CI); Barbara J. Burger, RN, CRNO, COT (CC); Jacqueline Anderson, COT (T); Gail Dempsey (T); Vivian F. Dzida, COA (OP,T); Jessica Musicant (T); Oscar Schnapp (T).

New York Eye and Ear Infirmary, New York, New York: Robert Ritch, MD (PI); Jeffrey M. Liebmann, MD (CI); Robert F. Rothman, MD (CI); Deborah Simon, COA (CC); Jean Walker (Asst. CC); Nancy Y. Gonzalez, COA (OP); Mark Johnson, COA (T); Bob Messina (OP); Alan Miller, COA (T); Sujata Nobotswing, OD, MS (T).

North Carolina. Wake Forest University Eye Center, Winston-Salem, North Carolina: L. Frank Cashwell, MD (PI); J. Brent Bond, MD (Co-PI); Joan Winnicki, RN (CC); Evelyn F. Andrew, COT (T); Marshall Tyler, BA, CRA (OP).

Ohio. Cole Eye Institute, The Cleveland Clinic Foundation, Cleveland, Ohio: Edward J. Rockwood, MD (PI); Laura M. Wash, COT (CC); Tami Fecko, COA (OP); Judy Hulse, COT (T); Mary Ann Peppard, COT (T); Deborah Ross, CRA (OP); Tom Thompson (T).

Oklahoma. Dean A. McGee Eye Institute, University of Oklahoma, Oklahoma City, Oklahoma: Gregory L. Skuta, MD (PI); Adam G. Reynolds, MD (CI); Angela Monlux, COT (CC); Carolyn Asuncion-Thompson, CRA (OP); Russell Burris, CRA, COT (OP); Cheryl Harris, COA (T); Joann Shannon (T); Janis Sims, COA (T).

Pennsylvania. Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania: Jody R. Piltz, MD (PI); Anna P. Singh, MD (CI); Jane L. Anderson, MS, CCRC (CC); Cheryl C. Devine, CRA (OP); Debra S. Elkins (OP); Cheryl A. Nathaniel (T); William Nyberg, CRA (OP); Janice Petner, BFA, COA (T); Laurel Weeney, CRA (OP).

Wills Eye Hospital, Jefferson Medical College, Philadelphia, Pennsylvania: George L. Spaeth, MD (PI); L. Jay Katz, MD (CI); Jonathan Myers, MD (CI); Donna M. Wittkowski, MS, COA (CC); Alaine J. Meli (T); Jeannie Molineaux, COA (T); Jamie Nichols, COPRA (OP).

Texas. Cullen Eye Institute, Baylor College of Medicine, Houston, Texas: Ronald L. Gross, MD (PI); Silvia Orengo-Nania, MD (CI); Benita Slight, COT, CCRA (CC); Pamela M. Frady, COMT, CCRC (OP, T).

Washington. Department of Ophthalmology, University of Washington, Seattle, Washington: Philip Chen, MD (PI, 1999–present); Richard P. Mills, MD (PI, 1993–1999); Howard S. Barnebey, MD (CI, Satellite Center); Martha Motuz Leen, MD (CI); Raghu Mudumba, MD (CI); Pat Ernst, BA, COA (CC); Carol Guenzler, RN, CRNO (CC, Satellite Center); Pendra Burrows, CO (T); Brad Clifton, BA (OP); Lori Grennan, COT (T); Ron Jones, BA (OP); James Leslie (OP); Susan Rath, COT (T); M. Chuck Stephens (OP).

Resource Centers

Administrative Center: University of Michigan, Ann Arbor, Michigan: Paul R. Lichter, MD (Study Chairman); Michael T. Bergiel, BBA (Grant Administrator); Mary Beth Donovan (Secretary); University of Kentucky, Lexington, Kentucky: Richard P. Mills, MD (Associate Chairman).

Coordinating Center: University of Michigan, Ann Arbor, Michigan: David C. Musch, PhD, MPH (Director); Kenneth E. Guire, MS (Deputy Director); Linda A. Cirenza (Secretary); Glen Feak, PhD (Programmer Analyst); Brenda W. Gillespie, PhD (Biostatistician); Mary L. Harper, BA (Database Administrator); Kathleen M. Pace, BS (Research Associate); Kelly A. Smid (Secretary); Carol L. Standardi, RN, CRNO (Protocol Monitor).

Interviewing Center: University of Michigan, Ann Arbor, Michigan: Nancy K. Janz, PhD (Director); Patricia A. Wren, PhD, MPH, MS (Deputy Director); Gail Stander (Secretary).

Project Office

National Eye Institute, Bethesda, Maryland: Donald F. Everett, MA (NEI Representative).

Study Groups

Data and Safety Monitoring Committee. Sheryl F. Kelsey, PhD (Chair); Anne M. Damiano, ScD; Frederick L. Ferris, MD; Paul Palmberg, MD, PhD; Kenneth W. Phifer, DMN; Alfred W. Rademaker, PhD; Angela Vela, MD. Ex officio members: Donald F. Everett, MA; Paul R. Lichter, MD; David C. Musch, PhD, MPH; Nancy K. Janz, PhD.

Steering Committee. Permanent members: Paul R. Lichter, MD (Chair); Donald F. Everett, MA; Nancy K. Janz, PhD; Richard P. Mills, MD; David C. Musch, PhD, MPH; Carol L. Standardi, RN, CRNO. Elected investigator members: Steven T. Simmons, MD (1993–1995); George L. Spaeth, MD (1995–1997); Henry D. Jampel, MD (1997–1999), Ronald L. Gross, MD (1999–present). Elected Clinic Coordinator members: Joan Winnicki, RN (1994–1996); Z. Suzanne Zam, BS (1996–1998), Laura M. Wash, COT (1998–2000), Rachel Scott, BS, COA (2000–present).

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