Revised Indications for the Treatment of Retinopathy of Prematurity

Results of the Early Treatment for Retinopathy of Prematurity Randomized Trial

Objective: To determine whether earlier treatment using ablation of the avascular retina in high-risk prethreshold retinopathy of prematurity (ROP) results in improved grating visual acuity and retinal structural outcomes compared with conventional treatment.

Methods: Infants with bilateral high-risk prethreshold ROP (n=317) had one eye randomized to early treatment with the fellow eye managed conventionally (control eye). In asymmetric cases (n=84), the eye with high-risk prethreshold ROP was randomized to early treatment or conventional management. High risk was determined using a model based on the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history cohort. At a corrected age of 9 months, visual acuity was assessed by masked testers using the Teller acuity card procedure. At corrected ages of 6 and 9 months, eyes were examined for structural outcome. Outcomes for the 2 treatment groups of eyes were compared using χ² analysis, combining data for bilateral and asymmetric cases.

Results: Grating acuity results showed a reduction in unfavorable visual acuity outcomes with earlier treatment, from 19.5% to 14.5% (P=.01). Unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. Further analysis supported retinal ablative therapy for eyes with type 1 ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. The analysis supported a wait-and-watch approach to type 2 ROP, defined as zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease. These eyes should be considered for treatment only if they progress to type 1 or threshold ROP.

Conclusions: Early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Additional analyses led to modified recommendations for the use of peripheral retinal ablation in eyes with ROP. Long-term follow-up is being conducted to learn whether the benefits noted in the first year after birth will persist into childhood.

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See also pages 1697 and 1769

(CRYO-ROP), the largest prospective trial of retinal ablative therapy for ROP, showed that 44.4% of eyes with a history of type 1 ROP that were treated with cryotherapy had a visual acuity of 20/200 or worse when children were tested at age 10 years. In children whose treated eye had a visual acuity better than 20/200, only 45.4% had a visual acuity of 20/40 or better. As a consequence, those involved in the care of infants with ROP have endeavored to find more effective approaches to treatment. One clinical trial, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study, showed no significant benefit to the use of supplemental oxygen therapy offered at a defined prethreshold point in the disease course. Another clinical trial, the Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) study, showed no benefit to preterm infants from a reduction in light exposure from birth to postmenstrual age 32 weeks.

In the CRYO-ROP study, peripheral retinal ablation was performed when the ocular findings indicated a risk of approximately 50% for retinal detachment. This degree of severity was termed the threshold for treatment of ROP and was defined as at least...
5 contiguous or 8 cumulative sectors (clock hours) of stage 3 ROP in zone I or II in the presence of plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph). During the past several years, the timing indications for treatment of ROP have been questioned, with some physicians advocating earlier treatment and others recommending conventionally timed treatment. A concern with earlier treatment is the expected increase in surgical intervention in eyes with ROP that would otherwise regress spontaneously. This concern has led to efforts to identify treatment selection criteria that will result in earlier treatment only in those eyes at highest risk for developing threshold ROP or an unfavorable visual or structural outcome in the absence of treatment.

In 1999, the National Eye Institute (Bethesda, Md) funded a cooperative agreement to study early treatment for ROP (Early Treatment for Retinopathy of Prematurity [ETROP] study). In the study, eyes of infants were randomized to early peripheral retinal ablation or standard (conventional) management if they developed prethreshold ROP and if RM-ROP2, a risk analysis program based on natural history data from the CRYO-ROP study, indicated a high risk of an unfavorable outcome. Prethreshold ROP was defined as zone I, any stage ROP that was less than threshold; zone II, stage 2 ROP with plus disease (dilation and tortuosity of posterior pole retinal vessels in at least 2 quadrants, meeting or exceeding that of a standard photograph); zone II, stage 3 ROP without plus disease; or zone II, stage 3 ROP with plus disease but fewer than 5 contiguous or 8 cumulative clock hours. Our article presents the findings of this study, including implications for the timing of retinal ablative treatment for ROP.

**METHODS**

Study protocols were approved by the review boards of all participating institutions, and parents provided written informed consent prior to infants' enrollment in the study and again at randomization. Infants with birth weights less than 1251 g and birth dates between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. Infants who survived at least 28 days underwent serial eye examinations, with the first screening examination occurring by 42 days after birth. If an infant developed ROP, parents were asked to consent to data collection and a possibly increased frequency of examinations. Study-certified ophthalmologists conducted serial examinations to detect rate of progression of ROP, development of prethreshold ROP, and development of threshold ROP. Infants with retinal vessels ending in zone I but no ROP or with zone II, stage 2 ROP received follow-up at least once per week. Infants with zone II, stage 1 ROP were examined at minimum every 2 weeks. If at least 1 eye reached prethreshold ROP, the infant's demographic and ROP information was entered into the RM-ROP2 risk model to determine the likelihood of progression to an unfavorable outcome in the absence of treatment.

**STUDY INTERVENTIONS**

Risk determination was made at the Coordinating Center using the RM-ROP2 model to evaluate data provided by each clinical center. If the risk of progression to an unfavorable outcome in the absence of treatment was calculated to be 15% or higher and a second examination by a masked study-certified ophthalmologist confirmed findings consistent with this risk, consent for the randomized trial was obtained and randomization occurred. Eyes that had a risk of 15% or higher were termed high-risk prethreshold. Eyes with less than a 15% risk were termed low-risk prethreshold and received follow-up every 2 to 4 days for at least 2 weeks until the ROP regressed or the risk progressed to 15% or higher. If both eyes were eligible for randomization, one eye was assigned at random to earlier treatment with ablative therapy within 48 hours of the first diagnosis of high-risk prethreshold ROP. Treatment generally consisted of laser therapy, but cryotherapy was also allowed. The fellow eye served as the control and was managed conventionally, which meant that it was observed until it either reached threshold and was treated or the ROP regressed without progressing to threshold. In cases in which only 1 eye reached high-risk prethreshold ROP, that eye was randomized either to treatment within 48 hours or to serve as a conventionally managed control, receiving treatment only if the ROP progressed to threshold severity. Infants in whom either eye developed threshold ROP prior to randomization were excluded from the study.

Infants born at nonstudy hospitals were eligible for the randomized trial if they were transferred to a participating center and were examined prior to age 42 days. If ROP was observed and reached high-risk prethreshold, consent was obtained and randomization occurred. Complete details concerning the study design and laser technique are described elsewhere (Early Treatment for Retinopathy of Prematurity Cooperative Group, unpublished data, 2003).

For the analyses, eyes with prethreshold ROP that remained low risk were categorized by the lowest zone and highest stage of ROP that developed. Eyes in the randomized group were classified according to the zone and stage of ROP that were present at the time of randomization, as determined by the confirming examiner's observations.

**FUNCTIONAL OUTCOME**

The functional outcome of each randomized eye at a corrected age of 9 months was evaluated with assessment of monocular grating acuity, conducted by 1 of 2 testers who were masked to the eye's treatment assignment and traveled to the study centers for testing. When possible, the grating acuity assessments were conducted on the same day as the 9-month follow-up examination. If not, these 2 assessments were done in close temporal proximity. The examining ophthalmologist was masked to grating acuity results at the 9-month examination.

The technique used to evaluate grating acuity was the Teller acuity card procedure, as performed previously in the CRYO-ROP study. The standard testing distance was 55 cm. Visual acuity was scored as the spatial frequency of the finest grating to which the infant showed a consistent fixation response. Eyes in which visual acuity was too poor to be quantified in this way were categorized as having no light perception (NLP), light perception only (LP), or detection of the grating on the low vision (LV) card only. The LV card has 2.2-cm-wide black-and-white stripes covering half of the card. It was used not to quantify vision but to determine whether the infant had pattern vision. The tester was permitted to move the LV card and present it at any distance or location in the infant's visual field.

Visual acuity data were included in the analyses only if the following criteria were met: (1) an acuity result (measurable acuity, detection of the grating on the LV card, LP, or NLP) was obtained for each eye in cases of bilateral high-risk prethreshold ROP or the randomized eye in asymmetric cases; (2) treatment for amblyopia, if present, had been prescribed for at least 4 weeks prior to the acuity test; and (3) refractive error, if present in either eye in cases of bilateral high-risk prethreshold ROP or the randomized eye in asymmetric cases, had been
corrected for at least 2 weeks prior to the acuity test. The criteria for correction of refractive errors were myopia greater than −4.00 diopters (D), hyperopia greater than +5.00 D, and astigmatism greater than 2.50 D in one or both eyes. Correction of anisometropia greater than 1.50-D spherical equivalent or 1.50-D cylinder was required only if the examining physician found evidence of amblyopia.

The visual acuity outcome was divided into 4 categories of functional response: normal, defined as greater than or equal to 2.00 logarithm of minimum angle of resolution (logMAR) acuity; reduced, defined as greater than 2.00 logMAR acuity; intermediate, defined as greater than or equal to 0.30 logMAR acuity; and blind/LV card. These functional outcome categories were further grouped into “favorable” (NLP, LP, or LV card) and “unfavorable” designations. The unfavorable grouping included eyes in the normal and below normal categories. The unfavorable grouping included eyes in the poor and blind/LV categories, which would be expected to have a poor long-term prognosis for visual function.16

**STRUCTURAL OUTCOME**

Structural outcome was documented with a dilated fundus examination at corrected ages of 6 and 9 months by study-certified examiners. Although examiners were instructed to refrain from seeking information about randomization assignment, they were not formally masked. Complete ophthalmologic examinations were performed at both of these ages; at the 9-month examination, a detailed examination of the data.

At the 6-month examination was conducted prior to the 9-month examination, eyes that had received a vitrectomy or scleral buckling procedure were classified for study purposes as having an unfavorable structural outcome.6

**STATISTICAL ANALYSES**

The ETROP study was designed to detect a 35% reduction in the percentage of eyes having an unfavorable structural outcome, with a type 1 error rate of 0.05 and a power of 80% (ETROP Cooperative Group, unpublished data, 2003). Using data from the CRYO-ROP study, the percentage of unfavorable eyes managed conventionally was predicted to be 20%. If earlier treatment produced a 35% reduction, 13% of these eyes would have an unfavorable outcome. Assuming that approximately 80% of infants were expected to have both eyes eligible for the study, the number of infants needed for the study was 370. The primary outcome measure for this study was visual function, for which there are limited data with which to conduct sample size calculations. Therefore, we based sample size on structural outcome. This was a conservative approach; in the CRYO-ROP study, unfavorable functional outcome rates were approximately 50% higher than unfavorable structural outcome rates for the ages at which functional outcome was tested.4,20,21

The statistical technique used to compare the eyes treated at high-risk prethreshold with the conventionally managed high-risk prethreshold eyes was developed and used in the CRYO-ROP study.22 It combines the data from infants with bilateral ROP (both eyes eligible) and those with asymmetric disease (1 eye eligible) into an overall χ² analysis of outcome differences between the 2 treatment groups. Although not part of the original study design, functional and structural results are also presented for International Classification of Retinopathy of Prematurity23 (ICROP) and RM-ROP2 categories to allow a more detailed examination of the data.

A Data and Safety Monitoring Committee of researchers, physicians, and an ethicist not directly involved in the ETROP study met in person every 6 months to review adverse event and outcome data and to monitor study progress. The committee approved the protocol and monitored the performance of participating centers. On the basis of their review of our findings, the committee voted in favor of expediting publication of the study results prior to completion of all 9-month follow-up examinations.

**RESULTS**

At the 26 clinical sites, 828 infants whose parents had given consent for systematic follow-up of ROP were identified as having prethreshold disease in 1 or both eyes. Among the 828 infants with prethreshold ROP, there were 499 (60%) whose eye or eyes were classified as high risk and who were thereby eligible for the randomized trial (Figure). Among these 499 infants, consent for randomization was not obtained for 40 infants, and high-risk prethreshold ROP was not confirmed by the required second study-certified examiner or for other reasons in 58 infants. Thus, 401 infants were enrolled in the randomized trial. The remaining 329 infants with prethreshold ROP judged to be low risk received the clinically indicated follow-up and then underwent follow-up study examinations at a corrected age of 6 months to determine retinal outcomes.

**Table 1** shows the distribution of prethreshold eyes by RM-ROP2 risk classification14 and by severity of prethreshold ROP according to the ICROP.24 One eye per infant, the eye with the higher risk according to the RM-ROP2 model, is represented in Table 1. This Table shows that the ICROP was a good indicator of most of the high-risk prethreshold eyes. For prethreshold zone 1 eyes with plus disease, 100% were high risk; when stage 3 was present without plus disease, 95.7% were high risk; and with stage 1 or 2 without plus disease, 92.3% were
high risk. In zone II, 95.2% of eyes that were classified as stage 3 with plus disease and 83.3% of eyes with stage 2 and plus disease were high risk, whereas only 8 (2.6%) of the 303 eyes that were zone II, stage 3 without plus disease were high risk. The parallels between the RM-ROP2 model and ICROP are particularly striking even though the former takes into account several demographic and disease-related factors that are not part of the ICROP.

Table 2 provides baseline characteristics for the 401 infants who entered the randomized trial. The mean birth weight was 703 g, and the mean gestational age was 25.3 weeks. At the time of randomization, 79.1% of the infants had bilateral high-risk prethreshold ROP according to the RM-ROP2 model. The remaining 20.9% of infants had asymmetric disease with high-risk prethreshold ROP in only 1 eye; the fellow eye had less severe ROP.

Table 3 shows the distribution of eyes treated at high-risk prethreshold and conventionally managed (control) eyes by ICROP categories at randomization, along with the percentage of conventionally managed eyes that reached threshold ROP. Zone I disease accounted for approximately 40% of randomized eyes. The largest categories of high-risk prethreshold ROP included eyes with zone II, stage 3 and plus disease (42.1% of earlier-treated prethreshold eyes and 43.7% of conventionally managed eyes) and those with zone I, stage 1 or 2 and no plus disease (27.4% of earlier-treated prethreshold eyes and 26.1% of conventionally managed eyes). Table 3 also indicates that 66.4% of eyes in the conventionally managed group progressed to threshold and underwent peripheral retinal ablation at that time.

The mean ± SD ages at high-risk prethreshold treatment were postmenstrual age 35.2 ± 2.3 weeks (range, 30.6-42.1 weeks) and chronological age 10.0 ± 2.0 weeks. The mean ± SD ages at treatment in the conventionally managed group for eyes that developed threshold ROP were postmenstrual age 37.0 ± 2.5 weeks (range, 31.9-46.6 weeks) and chronological age 11.9 ± 2.2 weeks. Anesthesia with intubation (routine at some hospitals) was used for 36.6% of infants who had high-risk prethreshold treatment compared with 30.9% when treatment was performed at thresh-

PRIMARY OUTCOME

Grating visual acuity data were obtained from 366 infants (96.6% of patients who survived). Data were not obtained from 22 infants who died prior to the 9-month examination, 8 infants whose parents did not bring them to the examination, or 5 infants who are waiting for visual acuity retesting because of uncorrected refractive error or amblyopia. Mean ± SD corrected age (age from expected date of delivery) at the time of grating acuity assessment was 10.3 ± 1.8 months.

Table 4 presents the proportion of randomized eyes with unfavorable grating acuity outcomes at 9 months. Over-
all, there was a significant benefit for the treatment of eyes with high-risk prethreshold ROP, with a reduction in unfavorable visual acuity outcome from 19.5% to 14.5% (P = .01). Within-subject comparison afforded a powerful opportunity to examine treatment effects while controlling for individual characteristics. Results from the 31 infants with bilateral ROP in whom there were discordant outcomes in the 2 eyes provide even stronger evidence of a beneficial effect of treatment at high-risk prethreshold (P = .007). Thirty-seven infants with bilateral high-risk prethreshold ROP had an unfavorable outcome in both eyes.

**Table 5. Distribution of 9-Month Grating Acuity Outcomes Among Randomized Eyes by Treatment Assignment**

<table>
<thead>
<tr>
<th>Eyes Treated at High-Risk Prethreshold (n = 330)</th>
<th>Conventionally Managed Eyes (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td></td>
</tr>
<tr>
<td>Normal (≥3.70 cycles per degree)</td>
<td>213 (64.5)</td>
</tr>
<tr>
<td>Below normal (1.85 to &lt;3.70 cycles per degree)</td>
<td>69 (20.9)</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td></td>
</tr>
<tr>
<td>Poor (measurable but &lt;1.85 cycles per degree)</td>
<td>15 (4.5)</td>
</tr>
<tr>
<td>Blind/LV (NLP, LP only, or LV card only)</td>
<td>33 (10.0)</td>
</tr>
<tr>
<td>Total</td>
<td>330 (100)</td>
</tr>
<tr>
<td>Conventionally Managed Eyes (n = 323)</td>
<td></td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>200 (61.9)</td>
</tr>
<tr>
<td>Below normal (1.85 to &lt;3.70 cycles per degree)</td>
<td>60 (18.6)</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td></td>
</tr>
<tr>
<td>Poor (measurable but &lt;1.85 cycles per degree)</td>
<td>16 (5.0)</td>
</tr>
<tr>
<td>Blind/LV (NLP, LP only, or LV card only)</td>
<td>47 (14.6)</td>
</tr>
<tr>
<td>Total</td>
<td>323 (100)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage). P = .001. As with grating acuity outcome, results from in-

en, fearful eyes randomized to high-risk prethreshold treatment than conventionally

managed eyes were designated as blind or LV (P = .08).

**SECONDARY OUTCOMES**

Structural outcome data were obtained from 366 infants (94.8% of patients who survived) at a corrected age of 6 months and 371 infants (97.9% of patients who survived) at a corrected age of 9 months. Six-month data were not obtained from 15 infants who died prior to the examination or 20 infants whose parents did not bring them to the examination. Mean ± SD corrected age at the 6-month examination was 5.5 ± 2.2 months. At 9 months, structural outcome data were not obtained from 22 infants who died prior to the examination or 8 infants whose parents did not bring them to the examination. Mean ± SD corrected age at the 9-month examination was 9.8 ± 1.4 months. This is younger than the mean age for visual acuity testing because the final acuity data were sometimes collected during retesting after the 9-month structural outcome examination.

The results for the 9-month structural outcome are presented in **Table 6**. Data indicate a statistically significant benefit for the treatment of eyes with high-risk prethreshold ROP, with unfavorable structural findings reduced from 15.6% in conventionally managed eyes to 9.1% in earlier-treated eyes with high-risk prethreshold ROP (P < .001). As with grating acuity outcome, results from infants with bilateral ROP in whom there were discordant outcomes in the 2 eyes provide strong evidence of a beneficial effect for treatment at high-risk prethreshold.

Among the 30 eyes treated at high-risk prethreshold that had an unfavorable structural outcome at 9 months, 2 had a partial retinal detachment involving the...
macula, 23 had undergone a vitrectomy or scleral buckling procedure, and 5 had a total retinal detachment. Among the 51 conventionally managed eyes with an unfavorable outcome, 4 had a partial retinal detachment involving the macula, 43 had undergone a vitrectomy or scleral buckling procedure, and 4 had a total retinal detachment.

Structural outcome results at the 6-month examination for eyes randomized at high-risk prethreshold were similar to those at 9 months, as indicated in Table 7. Six-month structural outcome data were also collected for low-risk prethreshold eyes (determined by the RM-ROP2 program to have <15% risk of an unfavorable outcome). Among this group of 329 infants, 51 (15.5%) had at least 1 eye that progressed to the conventional threshold for treatment and was treated accordingly. An unfavorable outcome occurred in only 4 (1.3%) of the 302 low-risk prethreshold eyes for which 6-month structural outcome data were available.

RELATIONSHIP TO ICROP CLASSIFICATION

Table 8 and Table 9 present the visual acuity and structural outcomes for randomized eyes stratified by ICROP category and RM-ROP2 risk category. The greatest benefit of treatment at high-risk prethreshold vs conventional management occurred in eyes that had zone I, stage 3 ROP with or without plus disease (30.8% unfavorable vs 53.8% unfavorable). A relative benefit from intervention at high-risk prethreshold for both visual acuity and structural outcomes was also seen among eyes that had zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP with plus disease.

As shown at the bottom of Tables 8 and 9, examination of outcome by RM-ROP2 risk category showed a greater benefit in both grating acuity and structural outcomes for earlier treatment in high-risk prethreshold eyes with a 30% risk or higher than in those with a risk of 15% to less than 30%.

OTHER OCULAR AND CLINICAL FINDINGS

The distribution of refractive errors at the 9-month examination was similar between the high-risk prethreshold eyes that received early treatment and those that were conventionally managed. Cataract or aphakia that was not associated with total retinal detachment or vitreectomy was found in 4 eyes (1.2%) in the group treated at high-risk prethreshold vs conventionally managed eyes (1.2%) in the conventionally managed group. Nyctalagus occurred in 22% of randomized infants with bilateral high-risk ROP.

Table 10 compares other ocular and systemic complications of treatment among infants treated at high-risk prethreshold vs conventionally managed infants in whom high-risk prethreshold ROP progressed and who later underwent treatment at threshold. Ocular complication rates were similar in the 2 groups. Systemic complications were higher following treatment at high-risk prethreshold. Infants with high-risk prethreshold ROP who were randomized to early treatment received peripheral retinal ablation at a mean postmenstrual age of 35.2 weeks compared with 37 weeks in conventionally treated infants who underwent peripheral retinal ablation at threshold.

This study of treatment for high-risk prethreshold ROP showed a benefit of earlier treatment compared with conventional management for the primary outcome measure of grating visual acuity at a corrected age of 9 months, as well as a much greater benefit for structural outcome at corrected ages of 6 and 9 months. Although the rates of ophthalmologic complications were similar among the 2 treatment arms, infants in the high-risk prethreshold group were more likely to experience systemic complications such as apnea, bradycardia, or reintubation following earlier treatment than with treatment at conventional threshold, perhaps because of the earlier mean postmenstrual age at which treatment was conducted. There was no mortality or known permanent morbidity attributed to treatment in either group.
The follow-up rate for visual acuity outcome was 96.6%, and for structural outcome it was 97.9%. The results indicate a benefit of earlier intervention for both visual acuity and structural outcome. The results support consideration for treatment of certain groups of eyes (type 1) with prethreshold ROP. Furthermore, the data clearly indicate that monitoring of ROP through serial examinations may be the better approach for other groups of eyes (type 2).

In the ETROP study, a novel risk model that was developed based on natural history data from the CRYO-ROP study was used to identify infants at high risk for adverse outcomes from ROP, and only those infants were randomized.\(^\text{10,11}\) The model used demographic characteristics of the infants and clinical features of ROP to classify eyes with prethreshold ROP as high risk or low risk. The validity of the model is demonstrated in the finding that high-risk prethreshold eyes that received conventional management had a much higher percentage of progression to threshold ROP than those at low risk (66.4% vs 15.5%, respectively) and a much higher percentage of unfavorable structural outcome (10% vs 1.3%, respectively, at 6 months). Eyes with low-risk prethreshold ROP were managed conventionally, with treatment administered if conventional threshold was reached. Overall, our study data support the treatment of selected eyes that develop prethreshold ROP.

In the CRYO-ROP study, only about 9.6% of eyes in the natural history cohort with prethreshold ROP had zone I disease; of these eyes, 33.3% had an unfavorable structural outcome.\(^\text{24}\) This strongly weighted the risk factor of presence of disease in zone I in the RM-ROP2 model. In the ETROP study, 22.7% of eyes with prethreshold ROP had zone I disease; because of the strong weighting of zone I ROP in the risk model, 94.7% of these eyes were classified as high risk.

### Table 8. Grating Acuity at 9 Months for Infants With Bilateral High-Risk Prethreshold Retinopathy of Prematurity by ICROP Category and RM-ROP2 Risk

<table>
<thead>
<tr>
<th>ICROP Classification</th>
<th>Eyes Treated at High-Risk Prethreshold</th>
<th>Conventionally Managed Eyes</th>
<th>Discordant Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zone</td>
<td>Stage</td>
<td>Plus Disease</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>3</td>
<td>Yes or No</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>1 or 2</td>
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<td></td>
<td>I</td>
<td>1 or 2</td>
<td>No</td>
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<tr>
<td></td>
<td>II</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>RM-ROP2 Risk</td>
<td>0.15 to &lt;0.30</td>
<td></td>
<td>108 (12.0)</td>
</tr>
<tr>
<td></td>
<td>0.30 to &lt;0.45</td>
<td></td>
<td>73 (13.7)</td>
</tr>
<tr>
<td></td>
<td>≥0.45</td>
<td></td>
<td>80 (22.5)</td>
</tr>
</tbody>
</table>

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity\(^\text{24}\); RM-ROP2, a risk analysis program based on natural history data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study.\(^\text{11}\)

*Data are presented as number (percentage unfavorable) unless otherwise indicated. High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph.

†For group A, earlier-treated eyes had a favorable outcome, and conventionally managed eyes had an unfavorable outcome.

‡For group B, earlier-treated eyes had an unfavorable outcome, and conventionally managed eyes had a favorable outcome.

### Table 9. Structural Outcome at 9 Months for Infants With Bilateral High-Risk Prethreshold Retinopathy of Prematurity by ICROP Category and RM-ROP2 Risk

<table>
<thead>
<tr>
<th>ICROP Classification</th>
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<th>Conventionally Managed Eyes</th>
<th>Discordant Pairs</th>
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<tr>
<td></td>
<td>Zone</td>
<td>Stage</td>
<td>Plus Disease</td>
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<tr>
<td></td>
<td>I</td>
<td>3</td>
<td>Yes or No</td>
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<td></td>
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<td>1 or 2</td>
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<td>II</td>
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<td></td>
<td>II</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>RM-ROP2 Risk</td>
<td>0.15 to &lt;0.30</td>
<td></td>
<td>109 (5.5)</td>
</tr>
<tr>
<td></td>
<td>0.30 to &lt;0.45</td>
<td></td>
<td>73 (9.6)</td>
</tr>
<tr>
<td></td>
<td>≥0.45</td>
<td></td>
<td>81 (18.5)</td>
</tr>
</tbody>
</table>

Abbreviation: ICROP, International Classification of Retinopathy of Prematurity\(^\text{24}\); RM-ROP2, a risk analysis program based on natural history data from the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Study.\(^\text{11}\)

*Data are presented as number (percentage unfavorable) unless otherwise indicated. High risk was 0.15 or greater. Plus disease was defined as a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph. Data include only those eyes for which structural outcome was able to be graded.

†For group A, earlier-treated eyes had a favorable outcome, and conventionally managed eyes had an unfavorable outcome.

‡For group B, earlier-treated eyes had an unfavorable outcome, and conventionally managed eyes had a favorable outcome.
risk, representing about 40% of eyes in the ETROP randomized trial.

The differences between the CRYO-ROP study and the ETROP study in frequency of zone I disease and regarding the more benign course of zone I ROP in the ETROP study are noteworthy. It is tempting to attribute the large number of zone I cases to advances in neonatal care and improved survival rates of the smallest premature infants. However, a thorough analysis (not presented in this article) of the data from the 2 studies (CRYO-ROP and ETROP) showed that even when the effects of birth weight and gestational age were controlled, the number of zone I eyes in the ETROP cohort was still significantly higher than in the CRYO-ROP study. Perhaps other changes in the care of premature infants, as yet unrecognized, have caused an increase in zone I disease and a decrease in its severity.

An alternative explanation is that examiners may now be more attentive to diagnosing zone I ROP than they were previously. The CRYO-ROP study showed a clear benefit of retinal ablative therapy, but the results in zone I eyes were not as impressive; most of these eyes developed unfavorable visual and structural outcomes even after receiving treatment at threshold. After publication of the CRYO-ROP results, it is possible that eyes were more carefully monitored and observed by ophthalmologists and that some eyes now diagnosed as having zone I ROP might have been categorized as zone II in the era before treatment proved effective. Additionally, some prior investigations considered posterior zone II eyes to be in the same category as zone I. An assignment of posterior zone II eyes to the zone I category might increase the number of zone I eyes in this study. These subtle factors could explain both the increased frequency and improved outcome of zone I eyes in ETROP subjects compared with CRYO-ROP subjects.

For all groups of eyes in the ETROP study, the effect of treatment at high-risk prethreshold was more pronounced for structural outcomes than for visual acuity outcomes. A similar discrepancy between the magnitude of difference between treatment groups for visual acuity vs structural outcomes was observed in the CRYO-ROP study. Because vision is the most important measure of treatment designed to prevent visual loss from severe ROP, the ETROP study chose visual acuity as its primary outcome measure. Also, there was a safety concern that treatment at high-risk prethreshold with laser could have a previously unrecognized deleterious effect on visual acuity. The Teller acuity card procedure was chosen as the assessment tool for measurement of visual acuity. The Teller acuity card procedure was not designed to detect prethreshold ROP. We discuss these issues as follows.

Another likely contributor to the difference between functional and structural outcomes in this study is the immaturity of the visual system at 9 months post-term. Because the visual acuity of a 9-month-old infant is lower than that of a healthy adult, certain visual deficits that result from structural abnormalities may not be apparent until an older age, when acuity in healthy eyes has improved to near-adult levels. Follow-up testing using recognition (letter) visual acuity charts at older ages would be expected to reveal these deficits in visual acuity, as it did in the CRYO-ROP study.

In evaluating the benefit of treatment at high-risk prethreshold, it is important to take into account possible adverse effects and trade-offs related to earlier treatment. These include an increased rate of systemic complications, potential long-term risks of earlier treatment, an increased frequency of treatment in eyes that would otherwise have undergone spontaneous regression of ROP, and an increase in the number of eye examinations needed to detect prethreshold ROP. We discuss these issues as follows.

In the ETROP study, systemic complications including apnea, bradycardia, and reintubation occurred more frequently when peripheral retinal ablative therapy was performed at high-risk prethreshold than at conventional threshold, probably because of the younger mean postmenstrual age at which the infants with high-risk prethreshold ROP were treated. Ophthalmic complications following retinal ablative therapy were comparable in eyes treated at high-risk prethreshold and conventionally managed eyes, as were ophthalmic complications (other than

<table>
<thead>
<tr>
<th>Complication</th>
<th>Eyes Treated at High-Risk Prethreshold†</th>
<th>Eyes Treated Conventionally at Threshold†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative ocular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival or subconjunctival hemorrhoma</td>
<td>30 (8.3)</td>
<td>16 (6.8)</td>
</tr>
<tr>
<td>Conjunctival laceration, unintended</td>
<td>16 (4.4)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Hemorrhage (retinal, preretinal, or vitreous)</td>
<td>14 (3.9)</td>
<td>12 (5.1)</td>
</tr>
<tr>
<td>Closure of the central retinal artery</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Inadvertent burn or freeze to area outside target zone</td>
<td>2 (0.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Systemic complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea, bradycardia, or arrhythmia</td>
<td>31 (8.6)</td>
<td>10 (4.2)</td>
</tr>
<tr>
<td>Acquired or increased cyanosis</td>
<td>13 (3.6)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Need for reintubation within 10 days of treatment after stopping artificial ventilation</td>
<td>40 (11.1)</td>
<td>12 (5.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage).
†Mean ± SD postmenstrual age at treatment in the early-treatment group was 35.2 ± 2.3 weeks and in the threshold treatment group was 37.0 ± 2.5 weeks.

Table 10. Complications Accompanying Treatment*
retinal detachment) when the entire group of conventionally managed eyes was compared with the group of eyes treated at high-risk prethreshold. One potentially deleterious effect of earlier treatment that was not evaluated in this study is that of peripheral retinal ablation on peripheral vision. It is possible that ablation in zone I will result in a greater loss in visual field extent than peripheral ablation in zone II.

Another issue related to earlier treatment of ROP concerns the treatment of eyes that would have undergone spontaneous regression without treatment. The following question arises: “How many eyes must receive treatment unnecessarily to achieve the benefit of earlier treatment for those eyes that need it?” According to the structural outcome data at 6 months for a cohort of eyes with prethreshold ROP of all degrees of severity that were conventionally managed, it is possible to determine the number of eyes with high-risk prethreshold ROP that had a favorable outcome without peripheral retinal ablation. The results are illustrated in Tables 11, 12, and 13.

The results are based on a natural history cohort of eyes from 664 infants who had 1 eye identified at prethreshold ROP that was not treated unless the ROP progressed to threshold. These results were used to consider the implications of alternative treatment strategies for managing prethreshold eyes. Included in this natural history cohort were all control eyes in the asymmetric randomized group, the conventionally managed eyes of infants with bilateral high-risk prethreshold disease, and 1 eye selected at random from the infants with low-risk prethreshold disease. Table 11 summarizes the results of an analysis of data from the natural history cohort of prethreshold eyes in the ETROP study. The Table shows that 136 (36.6%) of the 372 high-risk prethreshold eyes in the conventionally managed group that were examined at 6 months had favorable structural outcomes and never developed threshold ROP. In other words, these eyes met the criteria for early treatment, yet without treatment they had a favorable outcome at 6 months.

To reduce the number of eyes treated that would have had a favorable outcome without intervention, additional strategies for selecting eyes for earlier treatment were explored using this same cohort of prethreshold eyes. Table 12 gives the results for eyes classified by ICROP categorization, and it indicates that nearly 100% of zone I eyes were classified as high risk. However, eyes with zone I, stage 1 or 2 ROP without plus disease and eyes with zone II, stage 3 ROP without plus disease had lower rates of progressing to threshold or unfavorable outcome than eyes in the other ICROP categories. In addition, when treated at conventional threshold, those 2 groups of eyes had less than 5% unfavorable structural outcomes.

The results of this analysis along with the results in Tables 8 and 9 led to a clinical algorithm in which treatment should be considered for eyes with zone I, any stage ROP with plus disease; eyes with zone I, stage 3 ROP without plus disease; and eyes with zone II, stage 2 or 3 ROP with plus disease (type 1), with the remaining prethreshold eyes designated as type 2. The outcome results achieved by the proposed grouping of eyes, dividing the cohort into type 1 and type 2 ROP based on the ICROP classification, appear in Table 12. Use of this ICROP-based, limited-selection algorithm would have resulted in the treatment of 91 eyes that showed favorable outcomes and never reached threshold disease. This is a reduction of 33% from the 136 similar eyes that would have been treated using the RM-ROP2 risk model as applied in the ETROP study (Table 11).

If it is assumed that conventional threshold ROP continues to occur in 6% of infants weighing less than 1251 g at birth, as in the CRYO-ROP study, the early-treatment algorithm based on the RM-ROP2 program
Early Treatment Diabetic Retinopathy Study. Visual field definition visual acuity will be measured with charts from the ETROP study until age 6 years. At that age, recognition visual acuity will be measured using a revised treatment algorithm based on the eye findings of the ICROP alone.

Timely identification of prethreshold ROP is important to the successful application of an early-treatment program. In the ETROP protocol, infants received follow-up on a weekly basis after developing zone II, stage 2 ROP or if they had retinal vessels in zone I with vessels ending in zone 1 but no ROP in that zone. Infants with low-risk prethreshold disease received follow-up twice weekly and were treated conventionally unless a change in status caused by the development of more severe ROP resulted in advancement into the high-risk category. Thus, a screening program aimed at identifying eyes for treatment prior to the conventional threshold may require an increase in the number of screening examinations conducted in the neonatal nursery.

The long-term effects of earlier treatment for ROP are as yet unknown. Because visual acuity develops considerably between infancy and childhood and it is possible to measure aspects of visual function in childhood that are not easily assessed in infancy, the National Eye Institute has funded continued follow-up of randomized children in the ETROP study until age 6 years. At that age, recognition visual acuity will be measured with charts from the Early Treatment Diabetic Retinopathy Study. Visual field extent, contrast sensitivity, and ocular status will also be evaluated, and each child's developmental condition will be assessed. This longer follow-up period will give a more detailed evaluation of the effect of earlier treatment on the visual, ophthalmologic, and general developmental status of study participants.

### CONCLUSIONS

The results of this study show that it is possible to identify characteristics of ROP that predict which eyes are most likely to benefit from early peripheral retinal ablation. Based on study data, a clinical algorithm was developed to identify eyes with prethreshold ROP that were at highest risk for retinal detachment and blindness while minimizing treatment of prethreshold eyes likely to show spontaneous regression of ROP.

The use of this algorithm circumvents the need for computer-based calculation of low risk or high risk, as was used in this study. The clinical algorithm shows that in most circumstances, peripheral retinal ablation should be considered for any eye with type 1 ROP:

- Zone I, any stage ROP with or without plus disease
- Zone II, stage 3 ROP with or without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

Plus disease, in this instance, requires at least 2 quadrants (usually 6 or more clock hours) of dilation and tortuosity of the posterior retinal blood vessels and hence the presence of significant disease. The algorithm does not take into account all of the other known risk factors (eg, extent of stage 3 or birth weight), and therefore clinical judgment is required in applying this initial step to the management of ROP. The clinical algorithm also indicates that continued serial examinations as opposed to peripheral retinal ablation should be considered for any eye with type 2 ROP:

- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease

Treatment should be considered for an eye with type 2 ROP when progression to type 1 status or threshold ROP occurs.

Even with the addition of early treatment for selected eyes with prethreshold ROP, some eyes will still progress to an unfavorable visual and/structural outcome. Thus, additional research is needed to identify better methods for the prevention and treatment of severe ROP.

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Corresponding author and reprints: William V. Good, MD, Smith-Kettlewell Eye Research Institute, 2318 Fillmore St, San Francisco, CA 94115 (e-mail: Good @ski.org).

### REFERENCES


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ETROP Cooperative Group

Writing Committee
William V. Good, MD (chair); Robert J. Hardy, PhD; Velma Dobson, PhD; Earl A. Palmer, MD; Dale L. Phelps, MD; Michelle Quintos, BA; Betty Tung, MS.

Clinical Centers, Investigators, and Clinic Coordinators

Lucille Packard Children’s Hospital, Stanford University, Palo Alto, Calif: Ashima Madan, MD; Michael Gaymon, MD (co-principal investigators); M. Bethany Ball, BS; Patty Hartsell, RN, BA; Dottie Inguillo, RN (study center coordinators); Deborah Alcorn, MD; William V. Good, MD; Donna Ornitz, MD; David Stevenson, MD (co-investigators). California Pacific Medical Center, Children’s Hospital, University of California, San Francisco, Medical Center: William V. Good, MD (principal investigator); Monica Hubbard, MS, PNP; Jason Lee, MD (study center coordinators); Daniel Brinton, MD; Susan Day, MD; David Durand, MD; Douglas Fredrick, MD; Roderic H. Phibbs, MD; Daniel Schwartz, MD; Terri Slagle, MD; Gordon Smith, MD (co-investigators). University of Illinois at Chicago Hospital and Medical Center: Michael Shapiro, MD (principal investigator); Yesenia Garcia; Maria Genio; Jeffrey Parker; Bernadine Rupar (study center coordinators); Herbert Becker, MD; Rama Bhat, MD; Jeffrey N. Bloom, MD; Jessica V. Corsino, MD; Lawrence Kaufman, MD; Wico Waikwan Lai, MD; Jose Pulido, MD, MS; Michael Shapiro, MD (co-principal investigator);Ira H. Gewolb, MD (principal investigator); Kelly A. Hutcheson, MD (co-principal investigator); Loni Huyhn, COA; Rani Kalsi, BA, COA; Xiaonong Liu; L. Jennifer Smell, RN (study center coordinators); Susan J. Dulkierian, MD; Michael J. Elman, MD; Eric Jones, MD; Mark W. Preslan, MD; Scott M. Steidl, MD (co-investigators).
ETROP Cooperative Group (cont)

Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Greater Baltimore Medical Center, St Joseph Medical Center, Baltimore: Michael X. Repka, MD (principal investigator); Jennifer A. Shepard, NNP; Pamela Donahue, PhD (study center coordinators); Susan W. Aucott, MD; Tuvia Blechman, MD; Mary Louise Collins, MD; Maureen M. Gilmore, MD; James T. Handa, MD; Ananth Vijay Mudgil, MD; Quan Dong Nguyen, MD; Cameron F. Parsa, MD; Dante Pieramici, MD; David Plotsky, MD; Jeffrey J. Pomerance, MD (coinvestigators). New England Medical Center, Children's Hospital, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Lowell General Hospital, Lawrence General Hospital, Newton-Wellesley Hospital, South Shore Hospital, Melrose-Wakefield Hospital, Beverly Hospital, Boston, Mass: Cynthia H. Cole, MD, MPH (principal investigator); Deborah Vanderveen, MD (coinvestigator); Lacy Berman; Christy Faherty, RN, BSN; Caitlin Hurley, BS; Terry Mansfield, RN; Brenda McKinnon, RNC; Marianne Moore, RN (study center coordinators); Caroline Bauman, MD, FRCS; Amita Bhati, MD; Mark Dacey, MD; Jay Duker, MD; Janine Eagles, MD; Anthony Fraoli, MD; Paul Greenberg, MD; Mark Hughes, MD; Robert Lacy, MD; O‘rine McCabe, MD; Robert Peterson, MD; Elias Reichel, MD; Adam Rogers, MD; William Stinson, MD; Mitchell Strominger, MD (coinvestigators). William Beaumont Hospital, Children's Hospital of Michigan, St John's Hospital, Detroit, Mich: John Baker, MD (principal investigator); Kristi Cummins, MSN; Michelle Kulak, RN; Patrick Wall, MD (coinvestigators).

Fairview University Medical Center, Children's Health Care, Hemepine Medical Center, Minneapolis, Minn: Stephen P. Christiansen, MD (principal investigator); Sally Cook, BA; Ann Holleschau, BA; Mary Maxwell, RN; Marla Mills, RN, MSN; Carol Miller, RN; Kristin Rebertus, RN, NNP; Nancy Trower, RN, NNP (study center coordinators); Steven Bennett, MD; David Brasel, MD; Robert Couser, MD; Sundee Dev, MD; Allison Jensen, MD; Richard Lussky, MD; George Miller, MD; Robert Mittra, MD; Robert Ramsey, MD; William Rosen, MD; Timothy Olsen, MD; Robert Samuelson, MD; William Stinson, MD; Mitchell Strominger, MD (coinvestigators).

Cardinal Glennon Children's Hospital, St Mary's Health Center, St Louis, Mo: Bradley V. Davitt, MD (principal investigator); Julie Breuer, RN; Linda Breuer, LPN (study center coordinators); Oscar Cruz, MD; Stephen Feman, MD; William Keenan, MD; Ed Lang, MD; Greg Mantych, MD (coinvestigators). Duke University Medical Center, University of North Carolina Hospital, Durham, and Chapel Hill: Sharon Freedman, MD (principal investigator); Daniel Wallace, MD (coprincipal investigator); Eileen Camp, RN; Sharon Clark, RN; Lori Hutchins, RN; Lora Lake, RN (study center coordinators); Edward Buckley, MD; Laura Enyedi, MD; Ricki Goldstein, MD; Maurie Landers III, MD; Diane Marshall, MD; Travis Meredith, MD; Kean Oh, MD; Joan Roberts, MD (coinvestigators). Women's and Children's Hospital of Buffalo, Sisters of Charity Hospital, Buffalo, NY: James D. Reynolds, MD (principal investigator); Dawn C. Gordon, RNC; Barbara Kuppel, RN, BSN (study center coordinators); Michael A. Price, MD; Steven Awner, MD; Rita Ryan, MD (coinvestigators). Stony Brook University Hospital, Stony Brook, NY; Westchester Medical Center, Valhalla, NY: Pamela Ann Weber, MD (principal investigator); Adrienn Combs, RNC, Natalie Dweck, RN (study center coordinators); Howard Charles, MD; Tina Chou, MD; Joseph DeCristofoaro, MD; Corina Gerontis, MD; Marc Horowitz, MD; Richard Koty, MD; Edmund LaGamba, MD; Maury Marmor, MD (coinvestigators). New York Presbyterian Hospital (Columbia and Cornell campuses), New York: John Flynn, MD (principal investigator); Thomas Lee, MD (coinvestigator); Osode Coki, RNC, BSN (study center coordinators); Michael Chiang, MD; Steven Kane, MD; Alfred Krauss, MD; Robert Lopez, MD; Richard Polin, MD (coinvestigators). University of Rochester Medical Center, Rochester, NY; Crouse-Irving Memorial Hospital, Syracuse, NY: Dale L. Phelps, MD (principal investigator); Steven J. Gross, MD; David Hakanson, MD (coinvestigators); Marcia Dodge, RN; Cassandra Horihian, MS; Pamela Parker, BA; Jane Phillips (study center coordinators); Howard Charles, MD; Tina Chou, MD; Joseph DeCristofoaro, MD; Corina Gerontis, MD; Marc Horowitz, MD; Richard Koty, MD; Edmund LaGamba, MD; Maury Marmor, MD (coinvestigators). Columbus Children's Hospital, Ohio State University Hospital, Mount Carmel East Hospital, St Ann's Hospital, Columbus: Gary L. Rogers, MD (principal investigator); Don Bremer, MD (coinvestigator); Rae Fellows, MEd; Sharon Klambroth, LPN; Brenda Mann, RNC (study center coordinators); Richard Corden, MD; Richard Hertle, MD; Alan Leaton, MD; Richard McClellan, MD; Mary Lou McGregor, MD; Patrick Wall, MD (coinvestigators). Children's Hospital of Oklahoma, Oklahoma City: R. Michael Siatkowski, MD (principal investigator); Karen E. Corfie, MS, ARNP; Melissa Fuhr, RN (study center coordinators); Reagan H. Bradford, MD; Robert E. Leonard, MD; Mark H. Scott, MD (coinvestigators). Doernbecher Children's Hospital at Oregon Health and Science University, Legacy Emanuel Children's Hospital, Providence St Vincent's Hospital, Portland: David T. Wheeler, MD (principal investigator); Karen Davis, RN; Nancy Dolphin, RN; Sharon Dunham, RN (study center coordinators); Aaza Aaby, MD; Shawn Goodman, MD; Andreas Lauer, MD; Valerie Newman, MD; Earl A. Palmer, MD; De-Anne Pillers, MD, PhD; Joseph Robertson, MD; Ann Stout, MD; Tim Stout, MD; Andrea Tongue, MD (coinvestigators). The Children's Hospital of Philadelphia, the Hospital of the University of Pennsylvania, Pennsylvania Hospital, Philadelphia: Graham E. Quinn, MD, MSCE (principal investigator); Jamie G. Koh, RN, MSN, CCRC; Marianne E. Letterio, RN, BSN; Molly McDaniel, BA (study center coordinators); Soraya Abbasi, MD; Jane C. Edmond, MD; Brian J. Forbes, MD, PhD; Albert M. Maguire, MD; Monte D. Mills, MD; Eric A. Pierce, MD, PhD; Terri L. Young, MD (coinvestigators). Magee-Women's Hospital, Pittsburgh, Pa: Kenneth Cheng, MD (principal investigator); Judith Jones, RNC, BSN (study center coordinator); Robert Bergren, MD; Beverly Brozanski, MD; Bernard Dott, MD; Mitchell Fineman, MD; Louis Lobes, MD; Karl Olsen, MD (coinvestigators). Medical University of South Carolina, Charleston: Richard A. Saunders, MD (principal investigator); Lisa Langdale, RN (study center coordinator); Amy Hutchinson, MD; M. Millicent Peterseim, MD; Dilip Purohit, MD (coinvestigators). Baylor College of Medicine, Texas Children's Hospital, Texas Woman's Hospital, Ben Taub General Hospital, Houston: David K. Coats, MD (principal investigator); Laura Gonzalez; Natalya Kazymyrock, MD; Alma Sanchez, COT; Michele Seward, COT (study center coordinators); Kathryn Brady-McCreery, MD; Joseph Garcia-Prats, MD; Eric Holz, MD; Scott Jarriel, MD; Karen Johnson, MD; George Mandy, MD;
ETROP Cooperative Group (cont)

Evelyn A. Paysee, MD; A. Melinda Rainey, MD; Kimberly G. Yen, MD (coinvestigators). University Hospital, Christus Santa Rosa Children's Hospital, San Antonio, Tex: W. A. J. van Heuven, MD (principal investigator); Alice K. Gong, MD (coprincipal investigator); Melanie H. Drummond, RN (study center coordinator); Timothy Paul Cleland, MD; James C. MacDonald, MD; Lina M. Marouf, MD; Juan Elian Rubio, MD (coinvestigators). University of Utah Health Science Center, Primary Children’s Medical Center, Salt Lake City: Robert Hoffman, MD (principal investigator); Susan Bracken, RN (study center coordinator); Paul Bernstein, MD; David Dries, MD; Jerald King, MD; Richard Olson, MD; Michael Teske, MD; Kimberly Yen, MD (coinvestigators).

National Eye Institute, Bethesda, Md
Maryann Redford, DDS, MPH (program officer; June 2001 to present); Richard L. Mowery, PhD (October 2000 to May 2001); Donald F. Everett, MA (September 1999 to September 2000).

Study Headquarters
Smith-Kettlewell Eye Research Institute, San Francisco, Calif: William V. Good, MD (principal investigator); Michelle Quintos, BA (project coordinator).

Coordinating Center
School of Public Health, Coordinating Center for Clinical Trials, University of Texas Health Science Center, Houston: Robert J. Hardy, PhD (principal investigator); Betty Tung, MS (project manager); Charles Cooper, MS; Gordon Tsai, MS; Meng-Fen Wu, MS; Charles Minard, MS; Krystal Rather, BS (Coordinating Center staff).

Vision Testing Center
University of Arizona School of Medicine, Tucson: Velma Dobson, PhD (principal investigator); Graham E. Quinn, MD (coinvestigator); Kathleen M. Mohan, MA; Meigan B. Baldwin, BA (vision testers); Suzanne M. Delaney, PhD (Vision Testing Center coordinator).

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