

Nystagmus and Related Fixation Instabilities Following Extraction of Unilateral Infantile Cataract in the Infant Aphakia Treatment Study (IATS)

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PURPOSE. To study eye movements in a large group of children after the removal of unilateral infantile cataract, and to compare fixation instabilities between treatment groups with or without IOL implantation.

METHODS. The Infant Aphakia Treatment Study (IATS) is a randomized, multicenter clinical trial comparing IOL to contact lens (CL) treatment with a unilateral infantile cataract in participants who underwent cataract surgery at 1 to 6 months of age. At age 4.5 years, eye movements were recorded in 103 participants, using a high-speed video camera while the child performed a fixation task. The recordings were inspected by masked readers for the presence of fixation instabilities (nystagmus and saccadic oscillations).

RESULTS. Overall, fixation instabilities were observed in 50 (60%) of 83 children who had evaluable recordings, with no differences between treatment groups (27 [64%] of 42 in the IOL group, 23 [56%] of 41 in the CL group; $P = 0.51$). Nystagmus was seen in 38% and saccadic oscillations in 31%, with no differences between treatment groups ($P > 0.33$). Children without a fixation instability had better visual acuity ($P = 0.04$).

CONCLUSIONS. Nystagmus and saccadic oscillations are well-known consequences of infantile cataracts, presumably the result of visual deprivation during the critical period of visual development. After early cataract extraction, successful optical correction may reduce further form deprivation and minimize the incidence of these fixation instabilities. In this study, no differences in the presence of fixation instabilities were found between the two treatment strategies (CL or IOL) for optical correction after cataract removal. (ClinicalTrials.gov number, NCT00212134.)

Keywords: infantile cataract, nystagmus, fixation

Infants diagnosed with a visually significant cataract during the first few months of life are at risk for poor visual acuity, amblyopia, strabismus, nystagmus, or any combination of these. Prompt removal of the cataract(s) is indicated, with the goals of restoring a clear image on the retina and minimizing the impact of visual deprivation during the critical period of visual development. For dense congenital bilateral cataracts, studies have shown that earlier cataract removal is associated with better visual acuity outcomes.¹⁻³ Birch et al.² presented a regression model and concluded that, up to age 14 weeks, each 3 weeks of delay in surgery is associated with an additional 0.1-logMAR loss in visual acuity. Similarly, it was shown that for infants born with a dense unilateral cataract, surgery in the first 6 weeks of life is associated with a better visual acuity outcome.^{4,5} A further delay in surgery is associated with acuity outcomes deteriorating by approximately 0.35 logMAR for each doubling in age.⁴

Fixation instabilities (such as nystagmus and saccadic oscillations) are known consequences of infantile cataracts.⁶⁻¹⁰

In a cohort of 33 children with infantile cataracts covering a wide range of etiologies as well as a wide variation in the age at surgery, Abadi et al.⁸ found nystagmus occurring in up to 89% depending on subgroup. However, risk factors for poor ocular motor outcomes in children with cataracts have been studied less extensively than risk factors for visual function outcomes, usually regarding only the presence or absence of nystagmus^{11,12} (and/or strabismus¹²). The presence of nystagmus was shown to be associated with a worse visual outcome in children with dense bilateral congenital cataracts.¹¹ A recent study of children with dense cataracts from a variety of etiologies (congenital and developmental, bilateral and unilateral) found that infantile onset of a visually significant cataract was associated with nystagmus by age 5 years, and that the relative risk of nystagmus was higher in children with unilateral cataract than in children with bilateral cataract.¹² Furthermore, that study showed that prolonged duration of the cataract (>6 weeks) was associated with a significant risk for both strabismus and nystagmus (with odds ratios of 9.1 and 46.2, respectively).¹²

The Infant Aphakia Treatment Study (IATS) is a multicenter, randomized, controlled clinical trial sponsored by the National Eye Institute.¹³ The aim of the IATS is to compare the use of immediate IOL implantation with the correction of aphakia with a contact lens (CL) after cataract surgery performed in infants with a unilateral infantile cataract between 1 and 6 months of age. The visual function outcomes at age 4.5 years were not significantly different between the two treatment groups.¹⁴ However, significantly more intraoperative complications, adverse events, and additional intraocular operations occurred in the IOL group, especially in the first postoperative year.^{14,15}

The IATS provided us with the opportunity to investigate if, after early intervention, further benefits for ocular motor outcomes may occur with either one of the two strategies for optical correction. This article presents an overview of the fixation instabilities found in the IATS cohort at age 4.5 years, and compares the findings in the two treatment groups.

PATIENTS AND METHODS

Study Overview

The IATS study design, surgical techniques, follow-up schedule, patching and optical correction regimens, evaluation methods, and baseline patient characteristics have been reported in detail previously and are only summarized here.^{13,16} The IATS followed the tenets of the Declaration of Helsinki and informed consent was obtained from a parent or legal guardian of each of the participants after explanation of the nature and possible consequences of the study. The study protocol was approved by the institutional review boards of all participating institutions and was in compliance with the Health Insurance Portability and Accountability Act. The off-label research use of the Acrysof SN60AT and Acrysof MA60AC IOLs (Alcon Laboratories, Fort Worth, TX, USA) was covered by US Food and Drug Administration investigational device exemption #G020021.

The main inclusion criteria were as follows: a visually significant congenital cataract (≥ 3 mm central opacity) in one eye and an age of 28 days to younger than 210 days at the time of cataract surgery. Infants with a unilateral cataract due to persistent fetal vasculature (PFV) were enrolled in the study as long as the PFV was not associated with visible stretching of the ciliary processes or involvement of the retina or optic nerve. Other exclusion criteria were an acquired cataract, a corneal diameter smaller than 9 mm, a medical condition that might interfere with optotype visual acuity testing later in childhood, ocular disease in the fellow eye, and prematurity (< 36 gestational weeks). Patients were randomized to have either an IOL implanted at the time of cataract surgery or to be left aphakic and corrected with a CL.

Surgical Technique, Optical Correction, and Patching

Infants in the CL group underwent an extracapsular lensectomy, posterior capsulotomy, and anterior vitrectomy through the capsulotomy, whereas those in the IOL group initially had the lens aspirated followed by the implantation of an Acrysof SN60AT into the capsular bag. In the event that both haptics could not be implanted into the capsular bag, a different IOL (Acrysof MA60AT; Alcon Laboratories) was implanted into the ciliary sulcus after subtracting 1.0 diopter (D) from the calculated IOL power. Intraocular lens power targeted an 8-D undercorrection for infants 4 to 6 weeks of age and a 6-D undercorrection for infants older than 6 weeks. Following IOL

placement, a posterior capsulectomy and an anterior vitrectomy were performed through the pars plana/plicata.

Within a week after cataract surgery, infants in the CL group were fitted with a Silsoft (Bausch & Lomb, Rochester, NY, USA) or a rigid gas-permeable CL (per discretion of the investigator or the site-based contact lens specialist) with a 2.0-D overcorrection to provide a near point focus. For patients in the IOL group, spectacles were prescribed at or before the 1-month postoperative visit and/or at any later visit when one of the following conditions existed in the treated eye: hyperopia of more than 1.0 D, myopia of more than 3.0 D, or astigmatism of more than 1.5 D. The overall aim was to overcorrect the refractive error by 2.0 D to achieve a near point correction until the child was 2 years old. At that time, distance correction glasses with bifocals were prescribed for all patients, and patients were asked to wear them at all times while awake.

Starting the second postoperative week, parents were instructed to have their child wear an adhesive occlusive patch over the unoperated eye for x hours/day (where x equals the child's age in months), thus gradually increasing the amount of prescribed daily patching, until age 8 months. Thereafter, patching was prescribed for one-half of waking hours.

Follow-Up Examinations

Follow-up clinical examinations were performed by an IATS-certified, site-based investigator postoperatively at 1 day, 1 week, 3 months, and subsequently at 3-month intervals (± 2 weeks) until age 4.25 years to check for the appropriateness of the optical correction and to monitor for adverse events, and then at ages 4.5, and 5.0 years. Visual acuity was assessed by a masked traveling examiner at ages 12 months and 4.5 years.

Eye Movement Recordings

Eye movements were recorded at the age 4.5 years study visit, with the child seated in an examination chair in a dimly lit room, the head stabilized by means of a chin rest, and using a high-resolution (1280×512 pixels), high-speed (400 frames/second) video camera (Basler A504k; Basler AG, Ahrensburg, Germany) while the subject was fixating. A pair of low-intensity infrared illuminators (ISCAN, Woburn, MA, USA) was used to illuminate the face of the child. The child was instructed to look at a bright red light-emitting diode (LED) embedded in a black plastic board installed on a tripod at a viewing distance of 3 m (or 1.5 m if the room was not large enough). The size of the LED was 0.1° (at 3 m) or 0.2° (at 1.5 m). A second board at 33-cm viewing distance housed additional LEDs at 20° up, 20° down, 20° right, and 20° left from center, used for gain calibration. With the fixed focal length of the camera and a fixed distance from the subject, the gain factor was highly reproducible between subjects. One camera pixel corresponded to 0.1 mm of the child's face and to an eye rotation of 0.4° , representing the recording resolution and also the accuracy of the system.

Recordings were obtained with the child fixating the central LED target for approximately 7 seconds with the right eye, and then for approximately 7 seconds with the left eye, both times with an infrared filter occluding the other eye. The raw video data were stored on disc for off-line analysis. Using a multistep cross-correlation procedure, an algorithm tracked the x-y head drifts of salient elements of the face (away from the eyes) and shifted the image accordingly. The eye movement information relative to the head movement was then extracted using a pupil-tracking algorithm, filtered and differentiated to obtain the velocity traces. The eye position and velocity traces were extracted from the video data and de-identified.

Scoring of the Eye Movement Recordings

The results presented here are part of a multicenter trial, and testing was performed at each participating study site. A traveling examiner used portable equipment for the presentation of fixation stimuli and for the recording of eye movements. These factors, as well as the age of the participants (4.5 years at time of testing) and the fact that many wore glasses, posed a challenge on obtaining quantifiable eye movement recordings. As a result of these limitations, we decided that there were insufficient data to establish an outcome for each eye. Instead, a score was determined for each child by pooling the information from both eyes. A limited analysis on between-eye findings for the subgroup of children with data available from both eyes was also performed.

The recordings were read and analyzed by an eye movement expert masked to treatment assignment and treated/fellow eye for the presence of nystagmus¹⁷⁻¹⁹ and saccadic oscillations^{19,20} using published characteristics of these eye movement types. Saccadic oscillations were considered pathological if their frequency was more than 20 per minute or if they occurred in an obvious "burst." A child was recorded to have a fixation instability (i.e., nystagmus or saccadic oscillations) if the instability was seen in the recording of at least one eye. Children for whom evaluable recordings were obtained in only one eye were scored as "unknown" if that eye did not show the instability because the other, unreadable, recording might or might not have had the instability. The same method was applied to combine nystagmus and saccadic oscillations to determine a composite score for the presence of *any* fixation instability (nystagmus or saccadic oscillations). Subsequently, all recordings were examined by a second reader for the presence of fixation instabilities. Discordant interpretations were discussed by the two readers until a consensus was reached.

Statistical Analysis

The percentage of patients with a fixation instability was compared between the treatment groups using Fisher's exact test. Subgroup comparisons were performed using Fisher's exact test and the Wilcoxon rank-sum test.

RESULTS

A total of 114 infants were enrolled in the IATS from December 23, 2004, through January 16, 2009. Fifty-seven infants were randomized to each treatment group. Eye movement data were collected from 103 (90%) of the 114 children in the IATS. The remaining 11 children (6 in the CL group and 5 in the IOL group) were either not sufficiently cooperative for the test procedure or there was an equipment malfunction; one child missed the study visit.

The reader scored the presence of nystagmus and the presence of saccadic oscillations in each eye, or deemed the recording for the eye inevaluable if there was too much noise (due to, e.g., blinks, head movements, reflections, or low contrast). The recordings were considered evaluable for 167 eyes from 90 of the 103 children; 77 had both eyes evaluated, nine had only the fellow eye evaluated, and four had only the treated eye evaluated. Based on the scoring definition of "unknown" when evaluable recordings were obtained in only one eye if that eye did not show the instability (see Patients and Methods), the presence or absence of nystagmus was determined in 80 children, saccadic oscillations in 80 children, and the composite in 83 children (Table 1). For 19 patients (18%), the first and second masked reader came to a different

TABLE 1. Incidence of Fixation Abnormalities (Nystagmus and Saccadic Oscillations) Overall and in the Two Treatment Groups

Outcome	Overall	CL Group	IOL Group	P Value*
Nystagmus	30/80 (38%)	14/39 (36%)	16/41 (39%)	0.82
Saccadic oscillations	25/80 (31%)	15/40 (38%)	10/40 (25%)	0.33
Total (abnormality on 1 or both outcomes)	50/83 (60%)	27/42 (64%)	23/41 (56%)	0.51

* The *P* value for Fisher's exact test comparing the percentage of patients with an abnormality between the two treatment groups.

interpretation. Those patients were further discussed until a consensus was reached for all cases.

Among the 113 patients examined at age 4.5 years, there were no differences in either treatment assignment or visual acuity in the treated eye between patients who did and did not have evaluable eye movement recordings. Among the 30 patients without recordings or whose recordings were inevaluable, 15 (50%) were assigned to the IOL group compared with 41 (49%) of the 83 patients with recordings (*P* = 0.99). Median visual acuity in the treated eye was 0.70 logMAR (20/100) for patients without a recording and 0.90 logMAR (20/159) for patients with a recording (*P* = 0.81).

The median age at cataract surgery among the 83 children evaluated was 1.9 months (interquartile range, 1.1–3.2; range, 0.9–6.8). The mean age at the time of the eye movement recording was 4.5 years (SD 0.06; range, 4.5–4.9). Figure 1 presents examples of three children whose eye movement recordings show nystagmus, saccadic oscillations, and no fixation instability, respectively.

Nystagmus was seen in 14 (36%) of 39 children in the CL group and in 16 (39%) of 41 children in the IOL group (excluding "unknowns"), for an overall occurrence of 38% in this cohort (Table 1). Saccadic oscillations were seen in 31% of the children (15 [38%] of 40 in the CL group, and 10 [25%] of 40 in the IOL group.) For the composite of nystagmus and saccadic oscillations, 27 (64%) of 42 CL children and 23 (56%) of 41 IOL children had some type of fixation instability with an overall occurrence of 60% (50 of 83 children). The occurrence of the abnormalities did not differ significantly between the treatment groups (all *P* ≥ 0.33, Fisher's exact test).

Children with a cataract removed at age 6 weeks or younger showed similar rates of occurrence for nystagmus and saccadic oscillations as children with a cataract removed at a later age (see Table 2). Note that the occurrence of any fixation instability (nystagmus and saccadic oscillations combined) showed a tendency to be higher in the younger subgroup (*P* = 0.07).

A limited between-eyes analysis was performed in the subgroup of 77 children for whom the eye movements were evaluated in both eyes. Among them, 28 (36%) of the treated eyes (i.e., the eyes that had the cataract removed) showed a fixation instability, compared with 29 (38%) of the untreated fellow eyes (*P* = 0.86).

Median visual acuity at age 4.5 years was better (0.60 logMAR or 20/80) in the group of children without a fixation instability than in the group of children with fixation instabilities (1.20 logMAR or 20/320, Fig. 2). This difference was statistically significant (*P* = 0.04, Wilcoxon rank-sum test). However, when analyzed separately by type of fixation instability (nystagmus or saccadic oscillations), the subgroup differences in visual acuity did not reach statistical significance (*P* > 0.09).

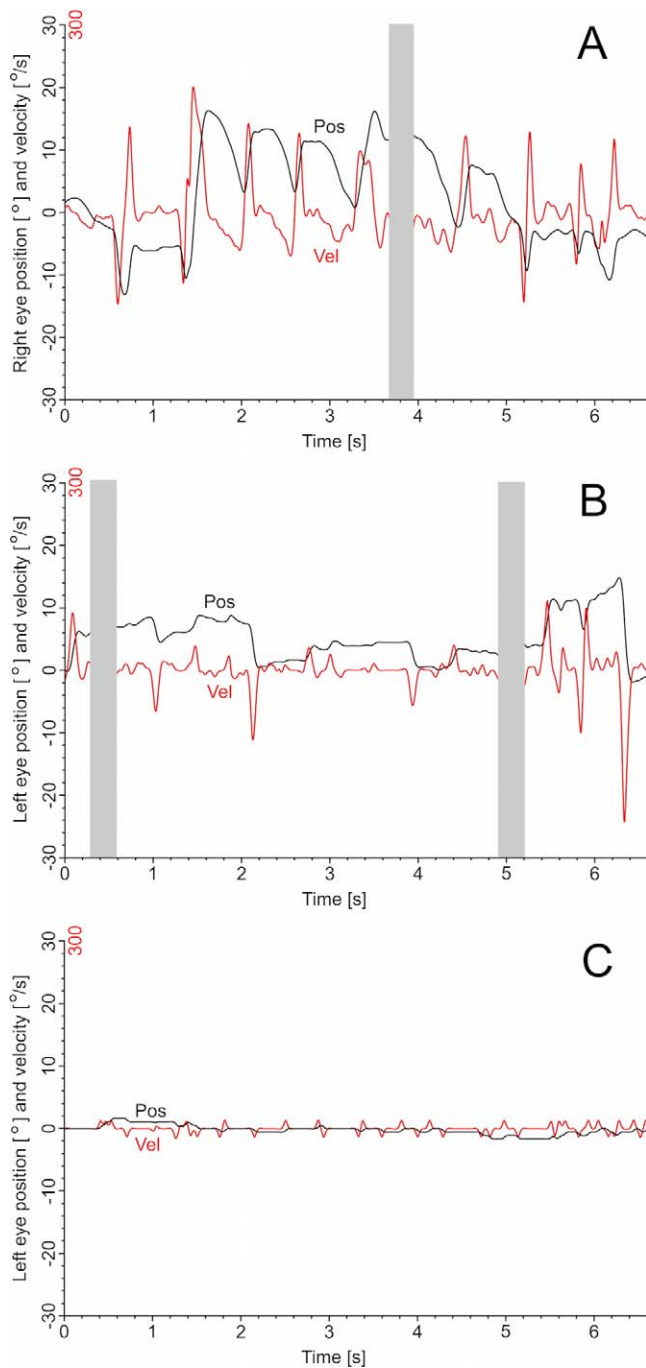


FIGURE 1. Examples of eye movement recordings from three patients. Each panel shows the eye position (*black traces*) and the eye velocity (*red traces*) of the horizontal eye movements. Vertical eye movements were recorded simultaneously but are not shown. (A) Nystagmus eye movements in the treated eye of child in the IOL group. (B) Saccadic oscillations in the treated eye of child in the IOL group. (C) No fixation instability seen in the untreated eye of child in the CL group. Gaps in the traces (*gray bars*) indicate blinks.

DISCUSSION

Nystagmus and saccadic intrusions are well-known sequelae of infantile cataracts.^{8,12,21} The fixation instability is presumably a consequence of the visual form deprivation during the critical period of visual development.^{8,21} After early cataract extrac-

TABLE 2. Incidence of Fixation Abnormalities (Nystagmus and Saccadic Oscillations) by Age of Cataract Removal

Outcome	Surgery at Age \leq 6 wk	Surgery at Age $>$ 6 wk	P Value*
Nystagmus	16/34 (47%)	14/46 (30%)	0.16
Saccadic oscillations	13/36 (36%)	12/44 (27%)	0.47
Total (abnormality on 1 or both outcomes)	26/36 (72%)	24/47 (51%)	0.07

* The *P* value for Fisher's exact test comparing the percentage of patients with an abnormality between the two subgroups.

tion, successful optical correction should prevent further form deprivation, which in turn may reduce the incidence of (unilateral or bilateral) amblyopia and fixation instabilities.

The follow-up phase of the IATS provided a unique opportunity to evaluate, in a relatively large nationwide cohort, whether the type of optical correction after cataract removal (CL or IOL) had a significant effect on the occurrence of nystagmus and saccadic oscillations. We found a similar incidence of fixation instabilities in the two treatment groups, overall averaging at 60%. Nystagmus occurred at a similar rate as saccadic oscillations.

Prompt and accurate optical correction after cataract removal during infancy, although challenging, has long been recognized as important for the prevention of deep amblyopia. In fact, the main rationale for conducting the IATS has been to investigate whether primary IOL implantation could avoid some of the known issues with contact lens correction (corneal problems, compliance with lens wear, lens loss, and so forth).¹³ At the visit at age 12 months, as well as at age 4.5 years, the two treatment groups showed no difference in the median visual acuity outcome.^{14,16} The current report shows that the occurrence of fixation instabilities was also similar in the two treatment groups.

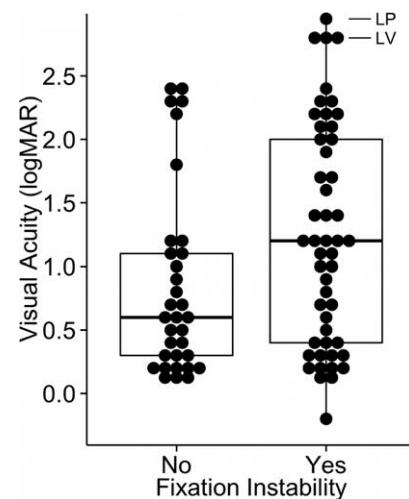


FIGURE 2. Boxplot of visual acuity in the treated eye for the two subgroups with ($n = 50$) and without ($n = 33$) a fixation instability in either eye. The *horizontal line* inside the boxes represents the median for each subgroup. There was a significant group difference ($P = 0.04$). *Black dots* represent the individual data. LP, light perception; LV, low vision Teller card.

Due to the limitations in data quality and the fact that eye movements were recorded only under monocular viewing conditions, no attempts were made to distinguish between nystagmus waveforms typical of fusion maldevelopment nystagmus (latent or manifest latent nystagmus) or infantile nystagmus syndrome (congenital nystagmus). Nevertheless, the overall incidence of nystagmus in the present study (38%) was lower than that reported by Birch and coworkers,¹² who reported nystagmus in approximately 70% of their subgroup of unilateral dense cataracts (see the online e-Supplement 2 for that article), and by Abadi and coworkers,⁸ who found nystagmus in approximately 60% of their subgroup with a history of unilateral major form deprivation. These differences may reflect different inclusion criteria. The study by Birch and coworkers¹² enrolled patients who underwent unilateral or bilateral cataract surgery during the first 5 years of life, whereas the IATS enrolled only patients who underwent unilateral cataract surgery during the first 6 months of life. Because nystagmus is believed to be more likely to develop in patients with bilateral cataracts and with longer periods of sensory deprivation, this may account for the higher incidence of nystagmus in the study by Birch and coworkers.¹²

Saccadic oscillations, also, were found to occur at similar rates in the two treatment groups. It should be noted that, although under these test conditions any nystagmus-type eye movements were considered “abnormal,” occasional saccadic oscillations are known to occur in normal observers. There are limited published norms available for these normal occurrences in the pediatric population.²²⁻²⁴ However, these all pertain to older children. Hence, a somewhat arbitrary cutoff rate was used to score the eye movement recordings for the presence of pathological saccadic oscillations. The main goal of the present analysis, however, was to compare the two treatment groups.

In the subgroup of children with evaluable recordings from both eyes, surprisingly, no significant differences were found between the occurrences of a fixation instability in the treated versus the untreated eyes. The numbers are small, however, and an important additional question: which of the two eyes shows poorer fixation instability, remains unanswered.

The presence of fixation instabilities was associated with poorer visual acuity. Two studies in children with amblyopia, using the bivariate contour ellipse area (BCEA) as quantitative measure of fixation instability, found conflicting results. Subramanian et al.²⁵ reported a significant correlation between BCEA and visual acuity for strabismic amblyopes as well as for their combined cohort of strabismic and anisometropic amblyopes, whereas Gonzalez et al.²⁶ found no correlation. In the present study, the difference in visual acuity between the groups of children with and without a fixation instability did not reach statistical significance. This may be partially due to a limited sample size in combination with binary outcome measures (presence/absence) for fixation instability. That 30 (27%) of the 113 patients examined at age 4.5 years did not have evaluable eye movement recordings further diminished our ability to find significant group differences. Comparing the 30 children without evaluable eye movement recordings with the 83 children with evaluable recordings found no differences with respect to treatment assignment or visual acuity in the treated eye. This suggested that there was no systematic bias for these factors between patients who did and did not have eye movement recordings.

In conclusion, the IATS found no differences in the presence of fixation instabilities between the two strategies (contact lens or intraocular lens) for optical correction of aphakia after the removal of a unilateral infantile cataract. The occurrence of nystagmus was relatively low compared with previous studies, possibly because all study patients in the IATS had their cataract removed before the age of 7 months.

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APPENDIX

The Infant Aphakia Treatment Study Group

Administrative Units

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Data Coordinating Center (Emory University): Michael Lynn, MS (Director), Betsy Bridgman, BS; Marianne Celano, PhD; Julia Cleveland, MSPH; George Cotsonis, MS; Carey

Drews-Botsch, PhD; Nana Freret, MSN; Lu Lu, MS; Seegar Swanson; Thandeka Tutu-Gxashe, MPH

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Harvard University, Boston, Massachusetts (14): Deborah K. Vanderveen, MD; Theresa A. Mansfield, RN; Kathryn Bisceglia Miller, OD

University of Minnesota, Minneapolis, Minnesota (13): Stephen P. Christiansen, MD; Erick D. Bothun, MD; Ann Holleschau, BA; Jason Jedlicka, OD; Patricia Winters, OD; Jacob Lang, OD

Cleveland Clinic, Cleveland, Ohio (10): Elias I. Traboulsi, MD; Susan Crowe, BS, COT; Heather Hasley Cimino, OD

Baylor College of Medicine, Houston, Texas (10): Kimberly G. Yen, MD; Maria Castanes, MPH; Alma Sanchez, COA; Shirley York

Emory University, Atlanta, Georgia (9): Scott R. Lambert, MD; Amy K. Hutchinson, MD; Lindreth Dubois, Med, MMSc; Rachel Robb, MMSc; Marla J. Shainberg, CO

Oregon Health and Science University, Portland, Oregon (9): David T. Wheeler, MD; Ann U. Stout, MD; Paula Rauch, OT, CRC; Kimberly Beaudet, CO, COMT; Pam Berg, CO, COMT

Duke University, Durham, North Carolina (8): Edward G. Buckley, MD; Sharon F. Freedman, MD; Lois Duncan, BS; B.W. Phillips, FCLSA; John T. Petrowski, OD

Vanderbilt University, Nashville, Tennessee (8): David Morrison, MD; Sandy Owings COA, CCRP; Ron Biernacki, CO, COMT; Christine Franklin, COT

Indiana University, Indianapolis, Indiana (7): David A. Plager, MD; Daniel E. Neely, MD; Michele Whitaker, COT; Donna Bates, COA; Dana Donaldson, OD

Miami Children's Hospital, Miami, Florida (6): Stacey Kruger, MD; Charlotte Tibi, CO; Susan Vega

University of Texas Southwestern, Dallas, Texas (6): David R. Weakley, MD; David R. Stager Jr, MD; Joost Felius, PhD; Clare Dias, CO; Debra L. Sager; Todd Brantley, OD

Case Western Reserve, Cleveland, Ohio (1): Faruk Orge, MD