Infant Aphakia Treatment Study
(IATS)
Phase 3 Study Protocol for the 10Y Visit

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CHAPTER 1 INTRODUCTION

The original purpose of the Infant Aphakia Treatment Study (IATS) was to assess the safety and the efficacy of IOL implantation in the rapidly growing eye of infants with a unilateral congenital cataract; children were randomized to either intraocular lens implantation (IOL) or contact lens (CL) correction following cataract surgery. Enrollment of the target sample size of 114 patients began in December 2004 and was completed in January 2009. Grating acuity was assessed at 12 months of age during Phase 1 of IATS and was completed in January 2010. Phase 2 began in March 2009. The optotype visual assessment was assessed during Phase 2 of the IATS when these children were age 4½ years using the ATS HOTV test. Phase 2 also included an ocular examination performed at age 5 years to evaluate: axial length, refractive error, keratometry, endothelial cell count, intraocular pressure, central corneal thickness and ocular alignment. At both the 1 Year and 4½ Year assessments, the visual acuity was found to be equal between the two groups. However, many more complications requiring additional surgery occurred in the IOL group, mostly in the first year after the initial surgery.

Glaucoma is one of the most serious adverse events that can develop after infantile cataract surgery. We did not find a significant difference in the cumulative incidence of glaucoma between the two treatment groups at age 5 years. We now postulate that newly diagnosed cases of glaucoma will occur more frequently between the ages of 5 and 10 years in the study eyes randomized to the CL group resulting in a higher cumulative incidence of glaucoma at age 10 years in this group. This hypothesis is based on a trend noted in the IATS between ages 1 and 5 years (new cases of glaucoma/glaucoma suspect: IOL group, 7 eyes (12%); CL group, 16 eyes (28%) and a study by Trivedi (Trivedi, 2006).

One of the unique challenges associated with primary IOL implantation during infancy is to select an IOL power that will optimize vision during infancy while not requiring an IOL exchange later in childhood. In the IATS, pseudophakic eyes were undercorrected by 8D (at 4-6 weeks of age) and 6D (at more than 6 weeks old) at the time of primary IOL implantation. At age 5 years, 3 eyes had undergone an IOL exchange because of a larger than expected myopic shift in the pseudophakic eye. We now postulate that additional pseudophakic eyes will require an IOL exchange after a longer follow-up. Following eyes randomized to IOL implantation to age 10 years, will allow us to identify risk factors for a large myopic shift and to determine the ideal undercorrection to optimize visual acuity while minimizing the need for IOL exchange. Phase 3 of this study intends to examine these children one additional time when they are 10 years of age. Longer follow-up will allow us to compare the long-term incidence and later onset of glaucoma in the study eyes in the two treatment groups and the rate of myopic shift so that risk factors for a larger than expected myopic shift can be identified in young children.

Study Aims:

1. Compare the cumulative incidence of glaucoma between the two treatment groups at age 10 years to determine which initial treatment is associated with the lowest long-term risk of glaucoma or glaucoma suspect.

2. Characterize myopic shift between the ages of 5 and 10 years in the IOL group.

3. Examine the impact of Unilateral Congenital Cataract on reading (speed, accuracy and comprehension), self-esteem and Health Related Quality of Life i

Background

At the time of our original proposal in 2003, IOLs were the accepted treatment following cataract surgery in older children and were being used increasingly in younger children (Wilson, 1996). However, among infants CLs were still the standard treatment since little was known about the safety of IOLs or the optimal IOL power to implant in a rapidly growing eye (Beller et al., 1981; Lorenz et al., 1991). Available data suggested that a fair-to-good visual acuity outcome could be more consistently obtained in infants with a unilateral congenital cataract who underwent IOL implantation at the time of cataract surgery (BenEzra, 1996; Dahan et al., 1997), but the methods used to assess the visual outcome in these series were non-standardized and may have overestimated the visual acuity of the pseudophakic eyes (Birch et al., 2005). Moreover, these series generally reported more complications in pseudophakic than aphakic eyes (Plager et al., 2002). Therefore, the question—What is the best way to treat infants with unilateral aphakia?—remained unanswered. The objective of IATS was to compare the visual outcome of two treatments for infants with a unilateral congenital cataract. The control group would receive the conventional treatment with a CL and later coupled with spectacle treatment. The experimental group would also undergo cataract surgery but in addition, would have an IOL implanted during the same surgery. The IOL would serve as the primary optical treatment. Any residual refractive error would then be corrected immediately with spectacles.

Given the expected 75-80 year life span of infants after cataract surgery and the impact that vision has on the quality of life, good vision in the cataractous eyes of children has the potential to have a major impact on their lives. Good vision in both eyes of these patients will allow them to pursue a broader range of professional and vocational opportunities and will give them the assurance that if they lose vision in their better seeing eye that they can continue to function as a sighted person. Reducing the incidence of glaucoma will also eliminate the discomfort and risks of having to undergo additional surgeries and/or daily medical therapy and the possible loss of vision in this eye later in life. While the prevalence of many complications can be established after a 5 year follow-up, the true prevalence of glaucoma following infantile cataract surgery cannot be established until after a longer follow-up. We chose a follow-up of age 10 years because most cases of glaucoma following infantile cataract surgery are diagnosed by this age. Thus, a 10-year follow-up of a well-characterized cohort should provide a more robust estimate of the impact of glaucoma on children treated for congenital cataract. In our own retrospective review of 62 eyes that underwent cataract surgery when <7 months of age, we found the 10-year risk of developing glaucoma or glaucoma suspect to be 63%.

The proposed research is expected to establish the optimal means of treating an infant following unilateral congenital cataract surgery to achieve the lowest incidence of glaucoma. In addition, exchanging an IOL requires that a child undergo general anesthesia with all of the attendant risks and costs. There are also ocular risks associated with additional intraocular surgeries. Accurately predicting the myopic shift after primary IOL implantation should reduce the need for IOL exchange.

Finally, the anesthesia associated with the standard care and treatment of surgical complications may result in a decrease in cognitive abilities. Children exposed to anesthesia before three years of age had lower scores in receptive and expressive language and cognitive ability than their peers (Ing et al.). Wilder et al, noted that children who had multiple anesthesia exposures prior to age 5 had significantly elevated risks of learning disabilities (Wilder). Another study noted that children who had surgery using general anesthesia within the first two years of life exhibited more behavior problems as teenagers.

IATS is a randomized clinical trial evaluating a large cohort of children who all underwent early cataract surgery using the same surgical protocols. After surgery, the children were examined at fixed time intervals using the same follow-up protocols. We had a 100% follow-up rate at age 12 months and a 99% follow-up rate at 5 years. In addition, the IATS developed a uniform definition of glaucoma with strict criteria. Intraocular pressure (IOP) was measured in all patients during an examination-under-anesthesia (EUAs) at age 12 months and at 4½ and/or 5 year examinations. Measuring IOP at follow-up examinations was made easier by the approval of ICare rebound tonometry (ICare Finland Oy, Helsinki, Finland) by the FDA in 2007. ICare rebound tonometry has been widely used in the IATS and it has greatly enhanced our ability to measure IOP in these young children in a clinic setting (Lambert, 2012). Previous studies reporting IOL implantation in infants have been small, retrospective case series (Autrata et al., 2005; Lundvall et al., 2006; Ram et al., 2011) with relatively short follow-up intervals and low follow-up rates. Finally, these other studies did not use a uniform definition of glaucoma and many relied exclusively on an elevated IOP to diagnose glaucoma. We expect the 10Y IATS visit to provide a more accurate assessment of the long-term effects of primary IOL implantation versus CL correction after unilateral cataract surgery during infancy on the cumulative incidence of glaucoma, the rate of axial length elongation, and the assessment of visual function.

In the Infant Aphakia Treatment Study (IATS), children with unilateral cataracts were exposed to anesthesia a minimum of two times in the first year of life as part of their standard of care. Many of these children had multiple other surgeries during this time period as a result of adverse events. For example, three-quarters of children in the IATS study had at least one additional surgery beyond the prescribed exam under anesthesia at twelve months of age, and over 90% of children who were randomized to receive an IOL at the time of cataract extraction had more intraocular surgeries as a result of adverse events, most commonly lens re-proliferation (68%) (Lambert et al, 2014). Before their fifth birthday, 44% of the IATS participants had had at least one additional surgery, not including surgery for strabismus (23-75%) and, to date, 3 of the 57 children randomized to remain aphakic had surgery to implant an IOL (Lambert et al, 2001).

Inclusion Enrollment Report

We enrolled 114 children in IATS between 12/04 and 1/09. All study patients were between the ages of 28 and 210 days at the time of enrollment. The patients all had a unilateral congenital cataract and the fellow eyes were normal. Only infants were enrolled in the study because our goal was to compare two optical treatments for infants following infantile cataract surgery. The ethnicity and gender of the patients enrolled in IATS is shown in Table 7. The clinical trial is being conducted at 12 clinical sites. The DCC and the chairman's office are located at Emory University.

Table 7: Ethnicity and Gender of Children Enrolled in IATS

Gender	White	Black	Am Indian/ Alaska Native	Asian	Other	Total
Female	**48**	**5**	**1**	**2**	**4**	**60**
Male	**49**	**3**	**0**	**1**	**1**	**54**
Total	**97**	**8**	**1**	**3**	**5**	**114**

Procedures

Glaucoma Evaluation

The incidence of glaucoma and the best surgical approach to minimize its occurrence after infantile cataract surgery are not known. The objective of this hypothesis is to compare the cumulative incidence of glaucoma after unilateral congenital cataract surgery with or without IOL implantation after a much longer follow-up. Glaucoma is one of the most serious complications occurring after infantile cataract surgery. A wide range of incidences of glaucoma has been reported following infantile cataract surgery (9% – 32% in 7 studies).

One large population based study estimated that the cumulative incidence of glaucoma in children <9 months of age at the time of cataract surgery was 32% after a 10 year follow-up (Haargaard, 2008). However, all of these studies had serious limitations. All were retrospective and many had a selection bias. Furthermore, some studies defined glaucoma solely on the basis of an elevated IOP (>25 mmHg) (Cotter, 2003; Swamy et al., 2007). Studies which relied solely on an elevated IOP to diagnose glaucoma may have over-diagnosed glaucoma, since there can be a long "lag" phase between modestly elevated IOP and clinically significant optic nerve or visual field damage in eyes with healthy nerves. In addition, the thicker corneas of aphakic eyes introduces a controversial but important potential source of measurement error in using IOP alone as a criterion for diagnosing glaucoma (Simsek et al., 2006; Muir et al., 2007; Lupinacci et al., 2009; Lim et al., 2011). Lastly, some of these series included patients that had undergone cataract surgery using outdated surgical techniques that may be associated with a higher risk of glaucoma than surgery performed using modern surgical techniques (Phelps et al., 1977; Chen, 2004).

Most studies suggest that a follow-up much longer than 5 years is necessary to determine the true cumulative incidence of glaucoma in eyes undergoing cataract surgery during infancy. In a population based study from Denmark the median time interval between infantile cataract surgery and the diagnosis of glaucoma was 6.6 years (25% quartile, 1.1 years; 75% quartile, 10.7 years) (Haargaard, 2008). Others have reported a mean interval of 7 years or longer from the time of cataract surgery until glaucoma was diagnosed (Mills et al., 1994; McClatchey, 1997). One study reported that the cumulative incidence of glaucoma almost doubled (11% to 19%) between the ages of 5 to 10 years (Egbert, 2006). Most studies of aphakic glaucoma are limited by a relatively short follow-up and as a result likely underestimated the cumulative incidence of glaucoma (Swamy, 2007; Chak, 2008; Kuhli-Hattenbach et al., 2008).
There is a debate in the literature whether primary IOL implantation following cataract surgery reduces the risk of glaucoma in pediatric eyes. Two large retrospective multi-centered studies have reported that glaucoma rarely developed in children following cataract surgery and IOL implantation. In the first study, only 1 of 377 (<1%) pseudophakic eyes developed glaucoma (mean follow-up, 5.1 years) compared to 14 of 124 (11%) aphakic eyes (mean follow-up, 7.2 years) (Asrani et al., 2000). However, none of the pseudophakic children in this study underwent cataract surgery during the first 12 months of life and the pseudophakic patients were older than the aphakic patients at the time of cataract surgery (5.06 vs 2.73 years) suggesting a selection bias. In the second study, only 1 of 105 (1%) pseudophakic eyes developed glaucoma compared to 89 of 377 (23%) aphakic eyes (hazard ratio, 0.036; 95% confidence interval, 0.001, 0.914; p=.044) after a mean follow-up of 5.92 years (Mataftsi et al,In Press). While all of the patients in this study underwent cataract surgery during the first year of life (median age, 3 months), it is likely that there was a selection bias for the children undergoing IOL implantation since it was a retrospective, non-randomized study.

In contradistinction to the studies by Asrani (Asrani, 2000) and Mataftsi (Mataftsi,2014), Trivedi and coworkers (Trivedi, 2006) did not find a statistically significant difference in the cumulative incidence of glaucoma after infantile cataract surgery with or without IOL implantation (24% vs 19%). However, the onset of glaucoma occurred earlier in eyes that underwent IOL implantation (median age of glaucoma onset, 3.5 months; range, 0.8 to 38 months) versus eyes that were left aphakic (median age of glaucoma onset, 90 months; range, 62 to 133 months). Glaucoma may develop earlier in infantile eyes after cataract surgery coupled with IOL implantation due to greater trauma to the trabecular meshwork at the time of cataract surgery. However, if glaucoma does not develop in the immediate postoperative period, the IOL may protect these eyes from developing glaucoma by mechanically supporting the trabecular meshwork or blocking the egress of toxic substances from the vitreous chamber to the trabecular meshwork. By following these children to age 10 years, we should be able to ascertain if the median age of onset of glaucoma is different between eyes that undergo primary IOL implantation versus eyes that are initially left aphakic after infantile cataract surgery.

Phase 3 Definition and Diagnosis of Glaucoma:

In Phases 1 and 2, an eye was defined as having ***glaucoma*** if the following criteria were present: IOP >21 mmHg with one or more of the following anatomical changes: 1) corneal enlargement; 2) asymmetrical progressive myopic shift coupled with enlargement of the corneal diameter and/or axial length; 3) increased optic nerve cupping defined as an increase of ≥ 0.2 in the cup-to-disc ratio, or 4) the use of a surgical procedure for IOP control. An eye was defined as ***glaucoma suspect*** if any of the following criteria were present: 1) two consecutive IOP measurements >21 mmHg on different dates after topical corticosteroids had been discontinued without any of the anatomical changes listed above; or 2) glaucoma medications were used to control IOP without any of the anatomical changes listed above.

In Phase 3, an eye will be defined as having ***glaucoma*** if the following criteria are present: 1) IOP > 21mmHg; and 2) a progressive increase in cup-disc ratio, cup-disc asymmetry of ≥ 0.2, or focal rim thinning. An eye will be defined as ***glaucoma suspect*** if any of the following criteria are present: 1) IOP > 21mmHg; or 2) glaucoma medications are being used to control IOP; or 3) an optic disc suspicious for glaucoma (e.g. increased cup-disc ratio). The criteria which will be used to diagnose glaucoma in Phase 3 will be the same as the criteria used in Phases 1 and 2 of the IATS, with the exception of ocular enlargement criteria. Unlike infants, children aged 5-10 years do not usually exhibit signs of ocular enlargement with elevated IOP. The criteria which will be used to diagnose glaucoma suspect in Phase 3 will also be the same as the criteria used in Phases 1 and 2 of the IATS with the exception that two consecutive IOP measurements >21 mmHg at two different visits will not be included in the definition since children in Phase 3 will only be examined once. In addition, since optic disc photographs will be taken at the 10Y exam, we have added a suspicious optic disc as another criterion for Phase 3. Since some children may be diagnosed as having glaucoma or glaucoma suspect between the five and 10 year evaluations, a review of medical records will be performed for all patients to determine who are classified as glaucoma or glaucoma suspect for Phase 3. This will assist in establishing diagnostic criteria and the age of onset for study purposes.

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Adult glaucoma studies typically include visual field criteria for the diagnosis of glaucoma. We have chosen not to include visual field criteria for the following reasons: 1) children usually cannot perform visual field testing until they are about 7-10 years of age; 2) initial visual field testing is unreliable in children; and 3) at least three visual field tests are needed to document a reproducible visual field defect.

Anterior Chamber OCT

Glaucoma in children is generally evaluated by measuring the intraocular pressure and assessing the cup-to-disc ratio of the optic disc. Gonioscopy, which is the "gold standard" in the evaluation of anterior chamber angles (Sharma R, 2013), is difficult to perform in children. Ultrasound biomicroscopy is another modality that has been used in children to assess the anterior segment of the eye. It uses ultrasound to image the anterior segment and studies have shown it to be consistent with gonioscopy. Its major disadvantage is that it requires an immersion shell to be placed on the eye which is generally not tolerated by young children. Due to its noninvasive nature, OCT may be useful for assessing the anterior segment of children after cataract surgery to evaluate risk factors for glaucoma as it is comparable to gonioscopy.

Nerve Fiber Layer OCT

Spectral domain optical coherence tomography (SD-OCT) has been shown to be a powerful tool evaluating and managing adults with glaucoma, and can even predict among glaucoma suspect those eyes at higher risk for developing visual field loss (Mwanza et al., 2011; Miki at al, 2014). In children, peripapillary retinal nerve fiber layer thickness (RNFL) assessed by either time domain OCT [Hess et al; Nadeau et al., 2010] or, more recently, by SD-OCT [Alasil et al, 2013], has been shown to be effective in differentiating between normal eyes and eyes with glaucoma (Ghasia et al., 2013; Srinivasan et al, 2014). RNFL measurements of both eyes will be taken using the Heidelberg Spectralis OCT by a trained OCT imager. Average RNFL will be compared between the surgical and the normal fellow eyes for all subjects. Average RNFL will be compared among study eyes with glaucoma suspect or glaucoma status, and those without a glaucoma-related adverse event. Quadrant level analysis of RNFL thickness will be carried out to detect trend in thinning among those with glaucoma-related adverse events compared to normal fellow and unaffected study eyes. Similarly, the difference in average RNFL between study and control fellow eyes will be compared for children with glaucoma suspect, glaucoma, and those with neither. Average RNFL will be correlated with optic nerve head cupping and the presence or absence of glaucomatous optic neuropathy (assessed by masked review of stereophotographs) across all study eyes.

Myopic Shift and Accuracy of IOL Calculations

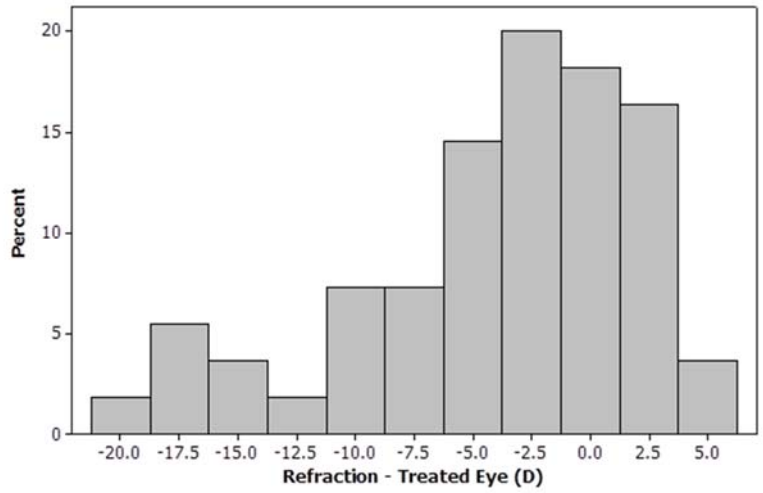
During childhood, the human eye elongates and the cornea and the crystalline lens flatten. When the biometrics of the growing eye are perfectly calibrated, the eye remains emmetropic. However, if the crystalline lens is removed surgically, the corneal flattening that occurs in early childhood cannot offset the 3-4 mm of axial elongation that occurs during the first year of life and the additional axial elongation that occurs in some eyes even into the teenage years.(Gordon et al., 1985) While small myopic shifts after IOL implantation can be corrected with contact lenses or spectacles, large myopic shifts may require an IOL exchange.(Dahan et al., 1990) In children with unilateral pseudophakia, a large myopic shift may contribute to the development of anisometropic amblyopia and impaired binocularity. Most clinicians undercorrect infants after cataract surgery and IOL implantation in anticipation of a myopic shift.(BenEzra, 1996; Dahan, 1997; Thouvenin et al., 2003; Autrata, 2005; Gouws et al., 2006) However, there is no agreement regarding the optimal magnitude of this undercorrection. While small cases series have reported a mean myopic shift ranging from 5 to 7 D after IOL implantation during infancy, these studies are retrospective with variable lengths of follow-up.(McClatchey et al., 2000; Ashworth et al., 2007; Astle et al., 2007) In addition, co-morbidities

such as glaucoma and microphthalmos which may impact the magnitude of the myopic shift were not always exclusion criteria in these studies.

In the IATS, all pseudophakic eyes had a targeted undercorrection of 6 or 8 D at the time of cataract surgery and primary IOL implantation (age 4-6 weeks, 8 D; age 7-28 weeks, 6 D). Postoperatively, follow-up clinical examinations were performed by an IATS certified investigator at 1 day, 1 week, 3 months and then at 3 months ± 2 weeks intervals until age 4 years and then at ages 4.25, 4.5 and 5 years. The age 5 year examination, included a cycloplegic refraction to assess the refractive error in both the treated and untreated eyes. The median (25th, 75th percentiles) refractive error in the treated eyes in the IOL group was -2.25 D (-7.25, 0.00) (range, -19.00 to +5.00 D). As expected, the median refractive error was larger in with glaucoma (-7.25 D) compared to eyes without glaucoma (-1.69 D).

	# Patients	Median	IQR*	Range
Without Glaucoma	44	-1.69	-5.03 to 1.16	-18.00 to 5.00
With Glaucoma	11	-7.25	-16.50 to -3.50	-19.00 to -1.50

Refractive Error at Age 5 Years for Patients Treated with an IOL



While the median refractive error was -2.25 D in the treated eyes in the IOL group, there was a wide range of refractive errors in these pseudophakic eyes at age 5 years ranging from +5.00 D to -19.00 D. The absolute prediction error was 1.8 D and only 41% of eyes had an absolute prediction error of 1 D or less. While the inaccuracy of the targeted refractive error was one factor, the unpredictability of the axial elongation of these eyes was the primary reason for the wide range of refactive errors at age 5 years.

Three eyes in the IOL group underwent an IOL exchange: one during the first postoperative year and 2 after the first postoperative year to correct refractive errors of -10.00, -8.50, and -19.00 D, respectively. None of these eyes had glaucoma.

CHAPTER 2 RESEARCH DESIGN and METHODS

The 114 patients enrolled in IATS will be examined within the year after their 10th birthday. A comprehensive ocular examination will be performed including tonometry and refractometry as well as measurements of central corneal thickness, keratometry, and axial length. Nerve fiber layer Optical Coherence Tomography (OCT) will also be performed. All data will be entered on standardized electronic Case Report Forms. All key personnel will maintain or acquire IATS certification according to the procedure described in the Manual of Procedures.

Informed Consent and Assent

At the 5Y visit, all caregivers were asked to give written permission for the study staff to maintain contact after the closeout visit. If the parents(s) or legal guardian(s) have agreed to have their child return for a study visit at age 10 years, the study will be discussed with them and with the child. Written informed consent must be obtained from the parent(s) or legal guardian(s) of the child before performing any procedures that are not part of the patient's routine care. In addition, because these children are now old enough to assent to their medical treatment, they must give verbal assent or sign an approved Assent Form. If the child has been followed by a non-study ophthalmologist since the 5y visit, the caregiver will be asked to sign a Medical Records Release form in order to capture the interim history.

The accompanying Caregiver will be asked to fill out a brief form regarding the child's use of optical correction, occlusion therapy, or special education services.

Retention

Attrition poses a significant threat to the internal validity of the proposed study given that attrition has been associated with low socioeconomic status and poor treatment adherence in chronic pediatric illnesses. The study group has been very successful in follow-up of the cohort and has experienced a very low attrition rate in both Phases 1 and 2 of the IATS. Nearly 90% of the mandated study visits were completed and more importantly, 100% of the Primary Outcome visits at age 12 months and 99% at age 4½ years were completed. All but 6 parents have signed a Permission to Contact Form allowing the Data Coordinating Center (DCC) to maintain contact with the participants and their parents even after they have completed the 5Y visit in Phase 2 of the study. Until mid 2015 the DCC will be maintaining contact with participants and their families in a variety of ways including: quarterly newsletters informing the families about key findings of the Study as well as providing information regarding visual development and ocular health, the popular IATS calendar, birthday cards, and periodic telephone contact with the families by the Site Coordinators. The DCC works to ensure that we have and maintain accurate addresses of the families, as well as contact information for other key individuals in each family's life. The Sites will begin trying to schedule the 10-year visit about 6 months in advance to ensure that there is adequate time to find any participants who may have moved and for whom there is not current address information available. In this case, the Clinical Coordinating Center and the Sites will collaborate to locate and retain these participants using available resources such as the family contacts and electronic search databases.

We will supplement our previously successful outreach programs using social media. Social media will provide us with another opportunity to engage participants and other interested stakeholders, and to inform these individuals about the Study's progress. Additionally, engaging participants has been an important component of our success in retaining participants.

Recent data suggest that 90% of Americans age 18 to 39 use the internet and 73% use social media, and that usage does not differ by race or ethnicity (http://www.pewinternet.org/2013/12/30/social-media-update-2013). The goal of including a social media presence in the IATS is to increase engagement with the Study and to enhance the sense of community among participants that was initiated through adherence phone calls, newsletters and calendars. We are adding this component to the proposed follow-up because of its increasing importance in American culture and because we will no longer be conducting adherence phone calls. Social medial will be used by IATS as a mechanism of engaging participants and creating a sense of community for these families, and not as a method to collect data or personally identifiable data. However, we will use social media to request that participants contact to Study to ensure that we have accurate contact information.

Because of recent trends in social media, as noted above, IATS will focus its social media presence on Facebook, Twitter and Pinterest which have high penetration among women aged 30 to 49. To ensure that these sites are used and serve the goals of the study, we will ensure that postings are updated at least three times each week. The postings will provide updates to the Study's progress, updates on publications related to the study, information of interest to parents with school-aged children and information of interest to caregivers of children with cataracts and other eye conditions which are prevalent among this population. All posts will be reviewed by the Executive Committee prior to posting to ensure that the most relevant and accurate information is presented. Additionally, best practices and guidelines developed by Federal agencies (i.e., CDC and NIH) will be used to govern the implementation of social media in IATS.

To encourage participation in the study, the following steps will be taken: 1) families will be reimbursed for the time they invest in the study visit with monetary incentives ($250 for attending the scheduled study visit and a $50 gift card for the child), 2) travel costs will be reimbursed if it is a financial hardship for families to return for the study visit, and 3) families will receive IATS newsletters three times a year and an "IATS Kids" holiday calendar annually.

Examination Schedule

Clinical examinations will be performed by IATS certified physicians and visits will be scheduled by the IATS certified clinical coordinator. Study visits will be scheduled for sometime in the year after children have reached 10 years of age and ideally around 6 months after the birthday. Non-study visits may be performed at the discretion of the investigator.

10.0 Years
Examination Information, Interim History, Reading
Manifest Refraction, Cycloplegic E-ETDRS Vision
Clinical Examination: Motility/Stereo, Biomicroscopy, Biometry/ keratometry, Tonometry, Pachymetry , Cycloplegic Refraction,
Imaging Optic Disc Photos, Nerve Fiber Layer OCT, Anterior Chamber OCT

CHAPTER 3. Clinical Examination

Primary Outcome Examination at Age 10 Years

A clinical examination will will be performed at age 10 years by the site investigator including biomicroscopy, retinoscopy, tonometry, and indirect ophthalmoscopy. Optical biometry, keratometry, and pachymetry will also be performed.
Visual acuity assessment using the E-ETDRS protocol will be performed by certified site personnel; patients should be in their best optical correction as determined by the PI either recently or just before the EVA test.

Discontinuation of CL Use Prior to Examination

If a child randomized to CL correction discontinues CL use prior to the age 10 year assessment and has not received a secondary IOL, then the child will wear the aphakic correction in a trial frame for the visual assessment or a CL with a close spherical power can be on hand and a trial frame can be used for residual correction.

Discontinuation of Spectacles Prior to Examination

If spectacles are still indicated for a child in the IOL group and the child discontinues their use prior to the age 10 year examination, the spectacles prescribed will be worn during the visual assessment. If the refraction has changed based on recent measurement or the glasses are not available, then the most current prescription in a trial frame can be used.

Manifest refraction

A non-cycloplegic measurement of the refractive error at distance will be performed on the study eye using a phoropter or a trial frame. If the child is wearing a contact lens, this refraction should be done *over* the contact lens. If the child is wearing spectacles, this refraction should be done *without* them.

Reading Test

We will use the ReadAlyzerTM to assess reading speed and comprehension (http://www.compevo.se/ReadAlyzerInfo.pdf). The ReadAlyzer system includes specialized goggles that are worn over the child's usual optical near correction. The near interpupillary distance is adjusted for the child's size. To ensure that the goggles are appropriately adjusted to the child, the child will read a short (100-word) passage written at the 1st grade level. If the child is unable to read and comprehend this short passage, the clinic staff will readjust the goggles to ensure proper fit. After proper fit has been ensured, the child will read a standard, grade-appropriate, 800-word passage and then answer a series of 20 comprehension questions. The system comes with software that provides automatic analysis of the number of fixations, the number of regressions, the mean fixation duration, the reading speed (words per minute), grade level equivalent and comprehension. There is no need for head fixation or calibration.

We have chosen to use the ReadAlyzer System in contrast to other standard reading systems such as the Gray Oral Reading Test (GORT) because it is relatively automated which should maximize inter-rater reliability, because it provides information on fixations and saccades

associated with reading and because it assesses silent reading which is salient to children's academic reading during the later years of elementary school.

Ocular Alignment and Randot Stereo testing

Ideally, testing of stereopsis should occur prior to occlusion of one eye for vision testing, motility evaluation, etc.

The Randot Preschool Stereoacuity Test measures random dot stereoacuity from 800 to 40 arc seconds. The test consists of three booklets. Each booklet has two sets of four random dot shapes on one page. One of these images is blank; the other three are pictures that can be seen only when viewed through polarizing lenses. On the opposite of the booklet are non-stereo images of the same shapes. There are six levels of stereoacuity in the test, with two levels in each book. Each level has four rectangles that contain three shapes and one blank.

Ocular alignment will be assessed with the child fixating on an accommodative target in the distance and at near using the simultaneous prism and cover test. The test will be performed by simultaneously covering the fixating eye and placing a prism in front of the deviating eye. Increasing prism powers are placed over the deviating eye until it no longer shifts. The power of the prism used when the deviating eye no longer shifts is the measure of the deviation. If the child cannot fixate on a target due to poor vision, increasing prism powers will be placed over the deviating eye until the pupillary light reflex is symmetrical with the pupillary reflex in the fixing eye (Krimsky test). If the child will not tolerate a prism placed over the deviating eye, a point source of light will be shown on both eyes. The angle of strabismus will then be estimated based on the degree that the pupillary light reflex is decentered relative to the fixing eye (Hirschberg light reflex test).

Biomicroscopy

An examination of the anterior segment will be performed using the slit lamp. In particular, the condition of the cornea, anterior chamber and, after dilation, the status of the media and IOL (if present) will be assessed.

Tonometry

Tonometry will be performed in both eyes at the 10Y study visit while the child is calm and quiet using Goldmann applanation tonometry preferably, but using Icare rebound tonometry (Icare Finland Oy, Helsinki, Finland), or Tonopen (Tono-PenXL, Medronic Solan, Jacksonville, FL), if necessary. Topical anesthesia is required for performing Goldmann and Tonopen tonometry, but is not needed for rebound tonometry. Rebound tonometry IOP readings on average measure 2 mm higher than Goldmann applanation tonometry (Lambert, 2013). In contrast, a Tonopen tends to underestimate high IOPs (Kooner et al., 1992). An alternative strategy would be to only assess IOP using Goldmann tonometry. However, some 10 year olds will not tolerate Goldmann tonometry, but will tolerate rebound tonometry or a Tonopen. Flemmons and coworkers reported that 3 of 17 children with glaucoma (mean age, 10 years) would not tolerate Goldmann applanation tonometry, but would tolerate IOP assessment using ICare or a Tonopen.

When Goldmann applanation tonometry is used, a drop of topical anesthetic mixed with fluorescein should be placed on the cornea. At least 2 measurements should be obtained that

are within 3 mm Hg of each other. If the readings are more than 3 mm Hg apart, then a third reading should be obtained. The average of the 3 IOP readings should be used as the study IOP. We anticipate that about 10% of the patients in our study will not tolerate Goldmann applanation and will require the IOP be measured with ICare or a Tonpen. If the IOPs obtained with ICare or a Tonopen are normal, no further testing will be performed. However, if the IOP is elevated (>21 mmHg) with ICare and/or Tonopen another attempt will be made immediately to measure the IOP using Goldmann applanation. If the child will still not tolerate Goldmann applanation, another attempt will be made 1-2 hours later after the child has had a lunch or snack and has rested. If the child will still not tolerate Goldmann applanation, arrangements will be made for the child return within 30 days to have the elevated IOP verified using Goldmann applanation. We anticipate that this scenario will occur in fewer than 5 patients.

When using rebound tonometry, the child should be sitting in a chair with the instrument positioned vertically. Icare rebound tonometry measurements should not be taken on a given eye until a long beep is heard, and the instrument panel shows a reliable IOP reading (with no error bar or the error bar on the bottom of the screen). If the error bar is in the middle of the screen, and the IOP reading is below 21 mm Hg, then this is also acceptable as a reading. At least two IOP measurements with reliable readings should be obtained within 3 mm Hg of one another, or a third reading should be taken and recorded. If the error bar is in the middle (with IOP above 20 mm Hg) or at the top of the screen, indicating a less reliable reading, the measurement should be repeated until a reliable reading has been obtained.

When using a Tonopen, the IOP reading should be taken with a 5% confidence interval noted on the instrument. At least 2 readings should be obtained within 3 mm Hg of each other. If the average IOP is > 21 mm Hg with ICare rebound tonometry or a Tonopen, a confirmatory IOP should be measured using Goldmann applanation tonometry.

Pupils

Pupils will be assessed for size (diameter in millimeters), shape (round or not), and position (central or eccentric).

Cycloplegic Refraction

A cycloplegic refraction of both eyes will be performed without external correction (ie, *not over contact lens or spectacles*) and using a phoropter or trial frame. Enough dilation should be achieved to accommodate later fundus imaging.

E-ETDRS Acuity Assessment after Cycloplegic Refraction

Monocular Visual Acuity Testing – Recognition Acuity

Visual acuity measures will be standardized at each clinical site by using the Electronic Visual Acuity Tester (EVAT). The EVAT runs a visual acuity testing program called E-ETDRS. This program was developed to provide a visual acuity letter score that is comparable to the ETDRS chart testing score. Visual Function Examiners (VFE) will have been certified to perform vision testing according to the protocol. Visual acuity will first be tested binocularly and then monocularly for each eye.

Electronic Visual Acuity Tester (EVAT)

The EVAT is an automated system that displays the acuity stimuli on a monitor. It uses a programmed Palm handheld device (or tablet PC) that communicates with a personal computer running a Linux (or Windows) operating system. This system was developed by JAEB for the ATS projects. Ten IATS sites use this system in their clinics; the other 2 sites have the E-ETDRS test available on the M&S acuity tester. VFE certification will occur via an online test at PEDIG sites and will be a paper test created by the JAEB Center for non-PEDIG sites.

Optical Correction

If the child was wearing a CL, the lens should be replaced on the study eye and any residual correction placed in a trial frame. Any correction needed for the fellow eye will also be placed in the trial frame. If the child normally wears spectacles, the vision should not be tested using them as there may be imperfections in the lenses. Instead the cycloplegic refraction should be placed in a trial frame.

Monocular Occlusion

A translucent occluder will be used to minimize the presence of latent nystagmus under monocular conditions. If this type of occluder is not available, an appropriate high plus power (e.g., +10D) lens may be used

Range of Testable Acuity

If the child is unable to see the largest (20/800) stimulus at the 3M testing distance, the testing will be conducted at 1 meter. The same procedure will be followed at 1 meter as was used at 3 meters. If the child is unable to detect the 20/800 stimulus at 1 meter (ie, VA < 20/2400), then the E-ETDRS testing will be stopped for this eye and the test for Hand Motion will be performed.

Assessment of Hand Motion Vision

The examiner's hand is extended to about two feet in front of the eye being tested; the fellow eye is occluded. With a light shining from behind the patient onto the examiner's hand, the hand is moved either up-and-down or side-to-side in front of the eye at a steady speed of about one cycle/second. The patient is asked to identify the direction of motion of five separate trials. Four out of five correct responses indicate the presence of Hand Motion vision. If fewer than four responses are correct, check for Light Perception vision.

Assessment of Light Perception

Children who are unable to perform E-ETDRS or Hand Motion testing in the treated eye will have that eye assessed for the presence of light perception (LP). LP will be tested with an indirect ophthalmoscope. Testing for LP will take place in a darkened room. Because the LP testing needs to be done monocularly, it is necessary to block the eye not being tested from all possible light to preserve accuracy. Standard eye patches alone do not achieve complete occlusion, and for this reason the tester, parent, or helper will place the palm of his or her hand gently but firmly over the patched eye thereby blocking out all light. The bright light from the indirect ophthalmoscope will then be directed at the uncovered eye 3 or 4 times from the front and sides at 18 – 24 inches from the face to avoid exposing the child to the heat of the light. The tester will ask the child to respond when the light is seen or to watch for consistent changes in

behavior occurring only when the light is being presented, such as eye movement towards or away from the light or head turn towards or away. If the examiner is convinced that the child does not perceive light, the vision will be recorded as No Light Perception.

Pachymetry

Pachymetry will be performed using the Pachmate (DHG Technology) or similar pachymeter after the instillation of a topical anesthetic drop. The probe tip will be touched to the center of the cornea and measurements will be taken until there is 1 with a SD <10 microns.

Optical Biometry

Axial Length

Biometry to determine axial length will be performed on both eyes using the non-contact instrument, the IOLMaster (Carl Zeiss Meditec, Dublin, CA) or Lenstar (Haag-Streit USA, Mason, OH). At least three measurements will be obtained for each eye and then averaged to hundredths of a millimeter. Both the raw data/scan and the summary page is to be printed out and faxed to the DCC.

Keratometry

Keratometry readings will be obtained using the IOLMaster or Lenstar. The AUTO mode will give the average of three measurements; two such averages should be obtained for each eye and their average recorded. Manual keratometry may be done if necessary.

Corneal Diameter

Corneal diameter will be taken from the IOLMaster or Lenstar biometry print-out.

Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed on the dilated eyes to determine the cup-to-disc ratio and to assess the health of the optic nerve and retina.

QUALITY OF LIFE MEASURES

Caretakers will be given a packet of questionnaires to take home. These are to be completed by either the primary caretaker or the study participant. They will be accompanied by detailed instructions and a stamped, addressed envelope for returning them to the Coordinating Center.

The questionnaires are:

Pediatric Quality of Life Inventory (PedsQL)
Effects of Youngsters' Eyesight on Quality of Life (EYE-Q)
Child Behavior Checklist
Self-Perception Profile for Children
Participation and Environment Measure for Children and Youth (PEM-CY)
Parenting Stress Index, Short Form (PSI-SF)

CHAPTER 4 IMAGING

Anterior Chamber OCT (AC OCT)

Anterior Chamber OCT will be performed on the undilated eyes. We prefer to use the Heidelberg SPECTRALIS spectral domain OCT machine. Heidelberg has created an anterior segment analysis lens and a specialized program. The Heidelberg SPECTRALIS anterior segment module, ASM, was approved by the FDA in March 2012 (Heidelberg Corporation, 2012). Leung et al. (Leung CK, 2008) found high reproducibility of results with the Heidelberg OCT along with agreement with gonioscopy findings. It is performed prior to instillation of any dilating drops.

Optic Disc Photos

Stereoscopic disc photographs are an established means of evaluating optic discs for glaucomatous damage. All patients will have stereoscopic disc photographs taken after dilating the pupils. Dilation will be performed prior to obtaining optic disc photographs. Simultaneous stereo images centered on the optic disc should be performed on both eyes using a digital fundus camera. The resolution of the disc photos should be such that the disc margins and vasculature are clearly visible. Disc photographs will be reviewed independently by three ophthalmologists with expertise in pediatric glaucoma (Sharon Freedman, Allen Beck, and David Plager). Photographs will be graded as normal, glaucoma suspect, or glaucomatous optic neuropathy primarily by comparing the appearance of the study eye to the fellow eye. Disc photographs were not part of the Phase 1 or 2 protocols due to the difficulty of obtaining high quality photographs in very young children.

Optic Nerve Fiber Layer OCT

Spectral domain optical coherence tomography (SD-OCT) has been shown to be a powerful tool evaluating and managing adults with glaucoma, and can even predict among glaucoma suspect those eyes at higher risk for developing visual field loss (Mwanza et al., 2011; Miki at al, 2014). In children, peripapillary retinal nerve fiber layer thickness (RNFL) assessed by either time domain OCT [Hess et al; Nadeau et al., 2010] or, more recently, by SD-OCT [Alasil et al, 2013], has been shown to be effective in differentiating between normal eyes and eyes with glaucoma (Ghasia et al., 2013; Srinivasan et al, 2014). RNFL measurements of both eyes will be taken using the Heidelberg Spectralis OCT by a trained OCT imager, with a baseline signal strength of at least 25. Average RNFL will be compared between the surgical and the normal fellow eyes for all subjects, the latter serving as the control group. Average RNFL will be compared among study eyes with glaucoma suspect or glaucoma status, and those without a glaucoma-related adverse event. Quadrant level analysis of RNFL thickness will be carried out to detect trend in thinning among those with glaucoma-related adverse events compared to normal fellow and unaffected study eyes. Similarly, the difference in average RNFL between study and control fellow eyes will be compared for children with glaucoma suspect, glaucoma, and those with neither. Average RNFL will be correlated with optic nerve head cupping and the presence or absence of glaucomatous optic neuropathy (assessed by masked review of stereophotographs) across all study eyes.

The OCT data will be submitted digitally so that they can be reviewed remotely without copy/fax/scan issues. Evaluation will consist of a look at the mean NFL, the superior/inferior/nasal/temporal quadrant numbers, and symmetry with the fellow eye.

CHAPTER 5 STATISTICAL CONSIDERATIONS & DATA CAPTURE AND MANAGEMENT

Study Design

IATS is a randomized controlled clinical trial with patients originally assigned to either CL or IOL as a correction for aphakia after cataract surgery. During Phases 1 and 2, investigators diligently avoided implanting a secondary IOL in patients randomized to CL correction except when it would be in the best interest of the child to have a secondary IOL because of lack of compliance with CL correction. Steering Committee approval was required before a secondary IOL could be implanted and documentation of the efforts to improve CL compliance had to be submitted before approval was granted. No child randomized to CL received a secondary IOL before the vision test at 12 months of age. As of December 2013 when all 57 study participants who were randomized to CL completed the study, only 3 had received a secondary IOL before the 5Y visit. Since the 5Y visit, 16 children in the CL group have received secondary IOLs.

Glaucoma

At age 1 year we did not find a statistically significant difference in the percent of patients with glaucoma/glaucoma suspect between the IOL and CL treatment groups (16% vs 9%, respectively, p = 0.39, 95% CI for difference = 6% - 21%). At 5 Years, those numbers were higher (CL 35% and IOL 28%), but were still statistically equal. We hypothesize that newly diagnosed glaucoma/glaucoma suspect will occur more frequently between the ages of 5 and 10 years in the study eyes randomized to the CL group resulting in a higher cumulative incidence of glaucoma in this group. The percent of patients with glaucoma at 10 years of age will be compared between the treatment groups using Fisher's exact test. As described above under the statistical considerations for visual acuity, we expect very little missing data. We will conduct sensitivity analyses comparing results for patients examined at 10 years of age with results in which patients not examined at 10 years who did not previously have glaucoma will be assumed to either have or not have glaucoma at 10 years of age. Patients not examined at 10 year of age who were previously diagnosed with glaucoma will retain that diagnosis in the sensitivity analyses, since per the IATS protocol, once a patient is diagnosed with glaucoma the patient is considered to have glaucoma for the remainder of the study.
We expect that the percentage of patients with glaucoma in treated eyes will double between the age 1 and 10 year examinations in the CL group whereas the percent will remain largely unchanged in the IOL group.

Myopic Shift

In the IATS, all pseudophakic eyes had a targeted undercorrection of 6 or 8 D based on age at the time of cataract surgery and primary IOL implantation (age 4-6 weeks, 8 D; age 7-28 weeks, 6 D). However, only 41% of eyes had an absolute prediction error of 1 D or less and the mean absolute prediction error was 1.8 D (VanderVeen et al., 2012). The myopic shift in these eyes was 0.53 D/month (95% CI; 0.42 to 0.63 D/month) until age 12 months and then 0.12 D/month (95% CI; 0.09 to 0.15 D/month) until age 42 months. From age 4 to 5 years, there was a mean myopic shift of 0.79 ± 1.56 D (range, -8 to +3 D). At age 5 years, the median (25th, 75th percentiles) refractive error in the treated eyes in the IOL group was -2.25 D (-7.25, 0.00) (range, -19.00 to +5.00 D). As expected, the median refractive error was larger in eyes with glaucoma compared to eyes without glaucoma. The variability in axial elongation was the primary reason for the wide range of refractive errors in these eyes at age 5 years (Lambert et al., 2012). Three eyes in the IOL group underwent an IOL exchange to correct a large myopic refractive error: one during the first postoperative year and 2 after the first postoperative year to correct refractive errors of -10.00, -8.50, and -19.00 D, respectively. None of these eyes had glaucoma.

Data Capture and Management

Data management procedures for this new phase of IATS have been designed with the following in mind: (1) Newly captured data will need to be integrated with the extensive IATS database from phases 1 and 2 in order to accommodate the scientific work needed to address the specific aims of the study, especially those involving longitudinal analyses; (2) many of the clinical center and Data Coordinating Center (DCC) staff from earlier phases of IATS will be working on the new phase; (3) FDA regulatory and reporting requirements will continue to apply to IATS, as they have in the past; (4) the development, refinement, implementation and maintenance of data management procedures must be efficient and streamlined, especially since the new phase involves just one clinical examination of each subject.

The DCC staff, data management programming and procedures for the new phase of IATS have been streamlined, and leverage the experience, existing infrastructure and resources of the current IATS DCC. Leveraging existing resources, rather than developing, implementing, refining and maintaining brand new systems for data management for the new phase that are separate from the systems for previous phases of IATS, is the most efficient approach, and is likely to have a direct and positive impact on data quality and scientific work in the study.

Data will be captured and managed using the latest, internet-based electronic data capture (EDC) modules that are part of Clinical DataFax Systems Incorporated's (CDSI) client-server data management software, iDataFax and DataFax (hereafter referred to as iDataFax). The data management system used in previous phases of IATS was based on earlier versions of the same CDSI software system, and is currently maintained by DCC staff using the latest version of this system. The DCC team that is in place is smaller than in past phases, but has extensive experience with CDSI's software, as is detailed in the sections below. Clinical center staff from the previous phases of IATS also have experience interacting with CDSI's data management system, especially in terms of receiving and responding to quality control reports generated by the system. The main difference for clinical staff in the new phase is that their data will be electronically entered into and captured by the system, instead of case report forms having to be faxed into it. The small amount of training that is required to become proficient in the use of CDSI's EDC module will be provided the DCC staff who have extensive experience in doing so.

Strict and extensive quality control programming and procedures are in place in the existing data management system for IATS. The continued use of CDSI's software, iDataFax, will allow for the programming and procedures to be efficiently extended into the new phase, will provide the best chance for maintaining the highest data quality, and will make it possible for us to continue to meet FDA regulatory and reporting requirements in the most efficient and rigorous manner.

<u>Data Capture, Flow and Handling</u>

A diagram of the systems for data capture, management and statistical reporting and analysis is shown in the "IATS Data Flow) figure below. The coordinator at each clinical site will record exam data on paper source document worksheets, and will then enter them into an electronic Case Report Form (eCRF) using the iDataFax EDC module installed on a local computer. The eCRF will look exactly like the source document worksheet, since the latter forms the background of the image on the EDC module screen into which the data are entered. The current drafts of the eCRFs and the source document worksheets will duplicate the eCRFs in format. The EDC module is able to connect to the main database on a server at the DCC, and will automatically store the data there in real time. Edit checks for data field validity will be applied at data entry time, and additional edit checks will be applied using nightly batch jobs running on the main server at the DCC. Any data issues will be marked by a query that describes the problem. Queries will be emailed to the clinical centers as a Quality Control Report (QC Report) on a monthly basis. Clinical coordinators fix most problems by making changes to the eCRF via the EDC module, which changes the query status from outstanding to

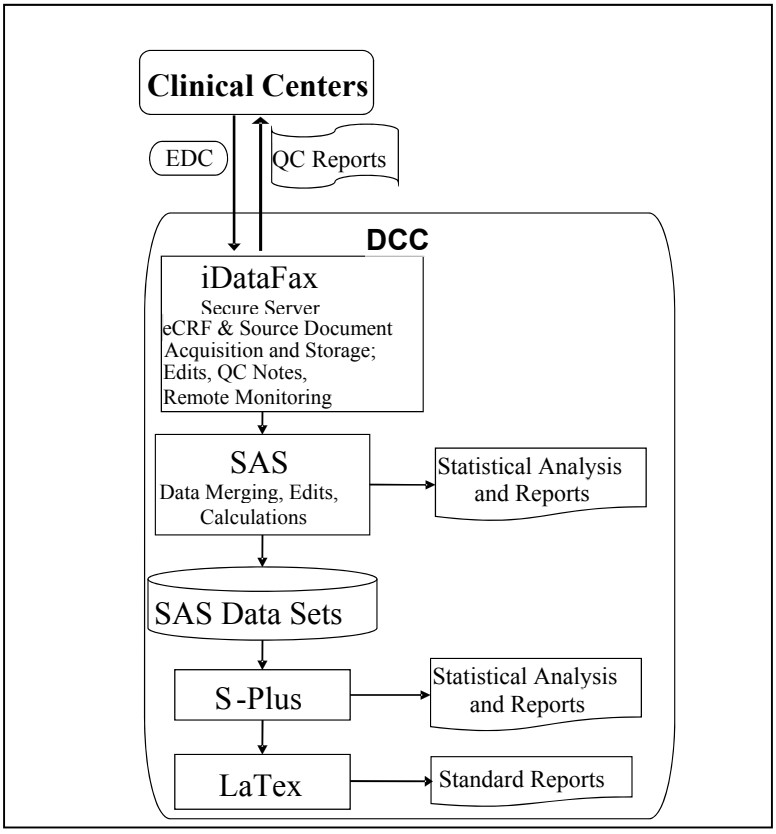
pending central review. The DCC clinical data manager will review the eCRF edits on a weekly basis and the queries will be either reinstated for further clarification or marked as resolved. iDataFax maintains an audit trail of eCRF edits made by both clinical center and DCC personnel.

Medical records such as clinical records related to adverse events and operative reports will also be submitted to the system via the EDC module as scanned images, which can be attached to the relevant eCRF page in the database.

For the purposes of remote monitoring of clinical sites, the clinical sites will upload scanned source document worksheets requested by the Clinical Data Manager at the DCC. The Clinical Data Manager will compare source document worksheets against electronically entered data. Discrepancies will result in queries being marked in the system, which will be included in the regular QC Report.

iDataFax can export data in forms that can be read by commonly used statistical analysis software packages. Daily exports from iDataFax will be performed by batch jobs running on the main server. Daily automated batch routines developed by the DCC Statistical Programmer will import the data into SAS data sets. These data sets will be used for standard analysis and reporting, performed on a weekly basis, for the purpose of providing information at regular executive and steering committee meetings. Department of Biostatistics and Bioinformatics personnel have developed a system of S-Plus functions that produce the code for making tables and graphs in LaTex, a mark-up language commonly used in mathematical fields for document processing. This system has been in use in previous phases of IATS, and will continue to be maintained, refined and used in this new phase for the purposes of producing standard reports for the FDA.

IATS Data Flow



Data Storage and Security

The electronically captured study data will reside exclusively on a secure, firewall- and password-protected Unix server at the Rollins School of Public Health (RSPH) of Emory University. The server is described in detail in the Facilities and Other Resources section of this grant application. It is housed in the locked server room of the RSPH, to which only certain staff members of the RSPH information technology (IT) group have keys. RSPH IT staff maintain the server, and perform daily incremental, and weekly full backups.

The data management system on the server will be accessed by IATS DCC staff from within the RSPH building via the school's secure internal network. At clinical centers, access to the EDC system will be limited to authorized personnel at the clinical centers (the center coordinator and PI), who will have access only to the data for their centers. The EDC module of iDataFax is compliant with all regulatory requirements including e-signatures, audit trails, and rules for password complexity, aging and notification. All changes to the database, at the data record and individual data field level, are recorded and include the id of the user making the change and the date and time of the change. The transmission of entered data and pdf files over the internet uses 128 bit SSL encryption.

Clinical Center Monitoring

Regular (weekly) Quality Control (QC) reports will be issued for each clinical center detailing eCRF data quality issues. DCC staff will continuously monitor eCRFs to ensure that

- all eCRFs are completed

- all eCRFs are up to date
- entered data are complete, accurate and follow study protocol and procedures.
- all eCRF corrections have been completed since last QC report

In addition to these weekly QC reports, we will implement a centralized, risk-based plan for remote monitoring of site study activities that is based on the specifications included in the "FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring" (US Department of Health and Human Services, Food and Drug Administration, 2013). The DCC Associate Director and Clinical Data Manager, in collaboration with the Study Chairman, will identify critical data elements and study administration or regulatory processes to be monitored and reviewed. At the Clinical Data Manager's request, the clinical sites will upload scanned source document worksheets and any other requested clinical or regulatory records using the EDC module of iDataFax. The Clinical Data Manager will compare source document worksheets against electronically entered data to review their accuracy, and will review and evaluate other uploaded documents as appropriate. Discrepancies will result in queries being marked in the system, which will be included in the regular QC Report. Remote monitoring of each clinical site will be performed on an ongoing basis.

Statistical Analysis

Descriptive analyses will be conducted to characterize the study population and detect potential selection bias as a result of missing data, dropouts or noncompliance/non-adherence. Two-sample t-tests will be used to compare continuous variables between two treatment groups. For continuous variables that are not normally distributed, appropriate transformations will be applied before normality-based tests are used or nonparametric tests such as Wilcoxon tests will be used as appropriate. Chi-square tests or Fisher's exact tests will be used to compare categorical variables between groups.

All primary analyses will be intention-to-treat. The percent of patients with glaucoma/glaucoma suspect at 10 years of age will be compared between the treatment groups using Fisher's exact test. We will also explore the role of baseline characteristics in the development of the primary endpoint using logistic regression and the Akaike information criterion (AIC; Akaike, 1974) will be used for model selection. In addition to analyzing the percent of patients who develop glaucoma/glaucoma suspect at any time up to age 10, we will also investigate analyzing the time to the primary endpoint using survival analysis methods, including the product-limit method to estimate the probability of developing glaucoma/glaucoma suspect versus time after surgery, comparing the time to developing glaucoma/glaucoma suspect between treatment groups with a log-rank test, and exploring the role of baseline characteristics with proportional hazards regression. The use of survival analysis methods may be problematic depending on how successfully we are able to determine the date of diagnosis, particularly for those patients who develop glaucoma/glaucoma suspect between 5 and 10 years of age when patients are not being examined within the study. Of note, patients not examined at 10 years of age who were previously diagnosed with glaucoma/glaucoma suspect will retain that diagnosis in all analyses, since per the IATS protocol, once a patient is diagnosed with glaucoma/glaucoma suspect the patient is considered to have glaucoma/glaucoma suspect for the remainder of the study.

As secondary analyses, we will repeat the aforementioned analyses for the secondary endpoint of glaucoma. In addition, we will use logistic regression for a multinomial outcome (proportional odds models or baseline logic models) to analyze the three categories, Glaucoma, Glaucoma Suspect, and normal (not glaucoma/glaucoma suspect) jointly.

Linear mixed models (LMMs) will be used to characterize the change in refractive error over time for both the treated and fellow eyes in the IOL group and to compare the changes in the treated eyes of the two treatment groups. In addition, LMMs will be used to identify baseline risk factors such as age of cataract surgery and axial length and other factors that arise during childhood, such as amblyopia and glaucoma, that are associated with a larger than expected myopic shift in the IOL group.

We will use two approaches for handling missing data as needed. First, we will use the available-case approach (Little and Rubin, 2002), i.e., conducting the proposed analyses excluding patients for whom the glaucoma/glaucoma suspect status is not verified at 10 years. Second, we will use the approach of multiple imputation (Little and Rubin, 2002) before conducting the proposed analyses and we will also conduct sensitivity analysis (Little et al., 2012). In addition, to correct for potential selection bias as a result of non-adherence to patching in early years and/or having a secondary IOL in the CL group, we will use approaches including instrumental variable and propensity scores (Little et al., 2009; Rosenbaum and Rubin, 1983). In addition, in case there are deviations from the target date for the outcome measurement, we will adjust for the time of the outcome measurement in our analyses as appropriate.

In addition to development of glaucoma, other clinical outcomes will also be measured and the analysis methods to be used in describing those outcomes are as follows.

Visual Acuity: For visual acuity at 10 years of age, we intend to use the Wilcoxon rank-sum test to compare the median visual acuities of the two treatment groups, with the patients included in the treatment group to which they were randomly assigned (intention-to-treat). As described in the section above **(**Status of Patients between Phases 2 and 3), among the patients randomized to CL who have thus far completed the 5 year of age exam, 38% have had secondary IOL implantation (insertion of an IOL after the initial cataract surgery). Thus, unlike in Phase 1 (1 year of age) when none of the contact lens patients had a secondary IOL and in Phase 2 (5 years of age) when only 2 contact lens patients had received a secondary IOL, for Phase 3 (10 years of age), a substantial percent of the patients in contact lens group will have a secondary IOL. Therefore, for visual acuity at 10 years of age, IATS will be a comparison between one treatment in which patients have an IOL inserted at the time of the cataract surgery and a second treatment in which patients are initially treated with a contact lens with the option of implanting a secondary IOL after 5 years of age. Analyses that attempt to address the question of a secondary IOL versus no IOL would likely be fraught with bias. Although the decision to have a patient undergo secondary IOL implantation is largely one of physician and parental preference, the condition of the patient is also a factor. For example, a secondary IOL would not be implanted in a patient with extremely poor vision. Therefore, such comparisons will be avoided.

In addition to the analysis to compare visual acuity at age 10 between the treatment groups, we will also investigate the relationship between baseline factors and the visual acuity at age 10. Since as described above we expect that visual acuity at age 10 will be skewed, for the multivariate analyses using linear regression, we will explore transformations of visual acuity to a less skewed distribution that also addresses the issue of lower threshold values for patients with extremely poor vision. Another approach we will investigate is categorizing visual acuity into 2 categories depending on whether or not the patient's vision is within normal limits (Driver et al., 2008) and using logistic regression to evaluate the relationship with baseline characteristics.

Adverse Events and Additional Ocular Surgery: The occurrence of adverse events and the need for additional ocular surgery will also be assessed (see the age 10 exam CRFs in Appendix 8). For those events and surgery that are specific to the IOL group, we will provide point and confidence interval estimates of the percent of patients experiencing those events. For events that apply to both treatments, we will apply the methods described above for glaucoma.

Ocular Alignment: The occurrence, type and extent of deviations will be described with basic descriptive statistics. Life table methods will be used to estimate the probability of being non-orthophoric at each of the follow-up visits and the development of strabismus over time will be compared between the treatment groups using the log-rank test. Patients who undergo strabismus surgery will be classified as non-orthophoric at the time of surgery

CHAPTER 6 Study Administration

Certification Procedures

All of the clinical coordinators and investigators were certified before beginning Phase 1 of the IATS using an online certification test administered by the JAEB center. All but two of the original IATS investigators continue to participate in the IATS. Both of these Sites had certified sub-Investigators who were approved to assume the role of PI.

Investigators

All of the current clinical site PIs have expressed a willingness to participate in Phase 3 of the IATS. No further certification will be required for current IATS investigators.

Coordinators

Site Coordinators who have already been certified will require no further certification. Personnel who will serve as new coordinators must take the certification exam administered by the JAEB Center.

Investigator/Coordinator Training

To accommodate the different “start” times for Phase 3, in lieu of a training meeting, we will have a repeatable online/conference call training session. All are welcome to attend the first presentation, but the coordinators at sites that will see their 10 year old patients who are nearing 11 years old in 2015 will be *required* to attend a presentation prior to the first 10Y visit.

Visual Function Examiners (VFEs)
Many of the IATS Sites are also PEDIG sites and have personnel who are certified to administer the E-ETDRS computer program (EVA) developed by the JAEB Center. Phase 3 will use these vision testers as the masked examiners. For those IATS Sites that do not have a PEDIG-certified VFE, the JAEB Center has agreed to provide a certification exam to a designated person or persons at the site (see Appendix 7). Each Site should have two (2) people designated as masked VFEs.

Study Organization

Projected Timeline for Phase 3 of the IATS

8/22/14 Visit window opens for Age 10 year examination of oldest patient

8/31/15 Funding for Phase 2 (Year 12) ends
9/01/15 Funding for Phase 3 begins

2/19/18 Age 10 year visit window opens for examination of youngest patient

Numbers of Patients Enrolled in the IATS who Become 10 Years of Age by Grant Year

Grant Year/Beginning Date	Phase 3 # (Age, 10 years)
Year 13 9/1/2015	52
Year 14 9/1/2016	35
Year 15 9/1/2017	25
Year 16 9/1/2018	2

Performance of Individual Sites

All of the individual sites have performed well in the study. On average, 91% of the expected follow-up visits have been completed to date. Most clinical sites have had patient follow-up rates >90%. Three sites have had patient follow-up rates near 80%; Baylor (81%); Emory (80%); and Indiana University (79%). The lower rates of expected follow-up visits at these clinical sites has largely been due to individual patients at these clinical sites who have been lost to follow-up or who have been difficult to follow. Only one patient was lost to follow-up at the 5Y visit.

Data Sharing Plan

Following NIH policy, the IATS investigators are submitting a plan for sharing final research data in line with the goal of making the data "as widely and freely available as possible while safeguarding the privacy of the participants and of protecting confidential and proprietary data" *. NIH policy also recognizes that "the investigators who collected the data have a legitimate interest in benefiting from their investment of time and effort".
The sharing of the IATS data will conform to the following considerations:

Patient confidentiality: All subject-specific data will be de-identified in the shared data files. In the IATS database maintained at the DCC, study patients are identified in the database by a unique 5-digit IATS ID Number consisting of a two-digit center number and 3-digit sequence number within the center. In shared databases the IATS ID will be stripped and a randomly generated sequence number will be assigned to each patient. The clinical center the patient was enrolled at will not be identified. Specific dates will not be included in the data file; rather, time intervals will be provided. The DCC will not share any patient health information listed among the 18 categories of direct identifiers that according to HIPAA regulations must be absent for a dataset to be considered limited.

Content and format of the data files: The content of the data files would be records, keyed by the randomly assigned sequence number described above, and containing the raw data values, subject to the privacy issues also described above. We will consider making the data available in a variety of formats, such as ascii files and Statistical Analysis System (SAS) transport files. Descriptions of the files will also be provided along with programming statements, such as the SAS Data Step code to input the data file.

Documentation: Documentation describing the conduct of the study such as the protocol, manual of procedures, and major published papers will be provided to lessen the likelihood that the definition of the data or how it was collected will be misunderstood or inadvertently misused.

Methods for release: At this time we are not specifying what form this will take since technological advances and future policy will impact our options. However, we will consider various possibilities including making the material available on the website of the Rollins School of Public Health of Emory University or submitting the material to a reputable repository for clinical trial data.

Timing of data release: Since IATS is a relatively complex trial, a large variety of data items will be collected. Making all items in the database available at once in conjunction with the publication of the first results paper is not prudent. We plan to make the data available in a series of releases after the publication of papers related to the pre-specified objectives and analyses. The files could be linked by the randomly assigned sequence number described above. The timing would be intended to coincide with the NIH policy that: "NIH continues to expect that the initial investigators may benefit from first and continuing use but not from prolonged exclusive use."

Licensing: At this time we do not expect to require any license agreements or data sharing agreements.

Responding to queries: Given the possibility that responding to queries regarding the data could be onerous, we do not plan to make such an offer when data is released.

* Quotations made in the text are from the NIH Data Sharing Policy and Implementation Guidance (Updated March 5, 2003) on the NIH Office of Extramural Research website at the address: http://grants.nih.gov/grants/policy/data_sharing_guidance.htm downloaded on 1/18/07.

Study Headquarters: The IATS chair's office is located in the Department of Ophthalmology at Emory University. The chair will be responsible for the overall supervision of the study.

Data Coordinating Center: The IATS Data Coordinating Center (DCC) is located in the Department of Biostatistics and Bioinformatics of the Rollins School of Public Health of Emory University and is responsible for the statistical and data management activities of the study. The School of Public Health is located only a few blocks from the Department of Ophthalmology.

Participating Clinical Centers:
Emory University, Atlanta, GA —PI, Scott Lambert
Harvard University, Cambridge, MA —PI, Deborah VanderVeen
Medical University of South Carolina, Charleston, SC —PI, M. Edward Wilson
Cleveland Clinic, Cleveland, OH —PI, Elias Traboulsi
University of Texas, Southwestern, Dallas, TX —PI, David Weakley
Duke University, Durham, NC —PI, Sharon Freedman
Baylor College of Medicine Houston, TX —PI, Kimberly Yen
Indiana University, Indianapolis, IN —PI, David Plager
Miami Children's Hospital, Miami, FL —PI, Stacey Kruger
University of Minnesota, Minneapolis, MN —PI, Erick Bothun
Vanderbilt University, Nashville, TN —PI, David Morrison
Oregon Health and Science University, Portland, OR —PI, Lorri Wilson

Executive Committee
The Executive Committee will be responsible for the day-to-day activities of the study and will meet weekly. The Executive Committee will organize all other committee meetings except for the DMOC and will be responsible for implementing changes in the Protocol and Manual of Procedures as needed. However, all substantive policy decision will be presented to the Steering Committee. The Executive committee will consist of the Study chair (Scott Lambert), the Director of the Data Coordinating Center (Qi Long), the Associate Director of the Data Coordinating Center (Azhar Nizam), the Data Manager (Seegar Swanson), the Epidemiologist (Carolyn Drews-Botsch), and the National Clinical Coordinator (Lindreth DuBois).

Steering Committee
The Steering Committee will approve all substantive changes to the Protocol and will review the progress of the study. They will ensure that there is agreement on the specifics of the Protocol and that it represents the clinical practice in different regions of North America. The Steering Committee will hold a conference call monthly. The Steering Committee will consist of all members of the Executive Committee and 3 additional clinical center Principal Investigators (Edward Buckley, David Plager, M. Edward Wilson), a pediatric glaucoma expert (Sharon Freedman), a Site Coordinator representative, and Donald Everett as an ex-officio representative from the National Eye Institute.

Writing Committee

The Writing Committee develops policies for the Study with regard to publication, initiates all primary outcome manuscripts, and participates in their authorship. An important responsibility of the Editorial Committee is to prioritize the use of Study data. This committee consists of the Study Chair (Scott Lambert, MD), the Director of DCC (Qi Long), the Associate Director of DCC (Azhar Nizam), Study Epidemiologist (Carey Drews-Botsch), and National Clinical Coordinator (Lindreth DuBois). All clinical investigators will be given the opportunity to serve as the lead author for at least one study publication. Approval will be obtained from the DSCM prior to publishing primary outcome data. The DMOC will also be kept informed of the publication of all secondary outcomes.

Investigators and Coordinators Group

This group will consist of all Principal Investigators and sub-Investigators, members of the Executive Committee, and all Clinical Coordinators. A group meeting will be held before the Phase 3 to familiarize investigators with the study protocol. Informational on-line meetings will be held with coordinators to familiarize them with the specifics of the protocol and data collection. An Investigator meeting will be held annually in conjunction with the annual meeting of AAPOS to review the IATS Phase 3 protocols and to discuss the progress of the study.

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Progress Report Publication List:

1. Lambert SR, Buckley EG, Drews-Botsch C, DuBois L, Hartmann E, Lynn MJ, Plager DA, Wilson ME and the Infant Aphakia Treatment Study Group. The Infant Aphakia Treatment Study: design and clinical measures at enrollment. Arch Ophthamol 2010;128:21-27. PMCID3230731.

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11. Carrigan AK, DuBois LG, Becker NK, Lambert, SR for the Infant Aphakia Treatment Study. Cost-Analysis of Intraocular Lens versus Contact Lens Treatment for a Unilateral Congenital Cataract. Ophthalmol In press. PMC--In process (Appendix 11).

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32. Celano MJ, Hartmann EE, Drews-Botsch CD. Motor skills of children with unilateral visual impairment in the Infant Aphakia Treatment Study. Submitted to Developmental Medicine and Child Neurology In revision

33. Drews-Botsch D, Cotsonis G, Celano M, Lambert SR. Assessment of Adherence to Visual Correction and Occlusion Therapy in the Infant Aphakia Treatment Study. J Clinical Trials Submitted

PROTECTION OF HUMAN SUBJECTS:

a. Study visit data will be recorded by the site coordinators on Source Document Worksheets which will be stored in a secure location at the site. The worksheets will be used by the coordinator to enter the data into the CDSI electronic data capture system used by the study, an FDA 21 CFR Part 11 compliant data management system capable of receiving data and documents via EDC, pdf email submission or fax. Clinical sites will be centrally monitored for protocol compliance and data quality by a Data Coordinating Center

b. The IATS clinical trial is registered with ClinicalTrials.gov Identifer: NCT00212134.

c. All of the patients in this clinical trial are children. Assent will be obtained from children and Informed Consent from parents prior to patients being enrolled in Phase 3 of the IATS (See Appendix 3).

d. There are minimal risks involved with an ocular examination using standard procedures. If the patient develops complications, we will make every effort to treat the complications in a manner which preserves the function of the child's eye.

e. The privacy of the patients will be maintained at all times. Assent and Informed Consent will be obtained before enrolling patients in Phase 3 of the IATS

f. If a patient develops complications, either the investigator will treat the patient or the patient will be referred to the most appropriate specialist in a timely manner. Data from the study are reported annually to the FDA and the DSMC. In addition, if serious adverse events arise, they will be reported to the institutional IRB by the investigator. The medical monitor for the IATS will also be notified and when appropriate he will then inform the DSMC regarding the complication.

g. The knowledge gained from the IATS should provide guidance on the most appropriate optical treatment to be used following infantile cataract surgery. In addition, information should be gained on what is the most appropriate IOL power to implant in an infantile eye and the likelihood of certain complications. This information may be generalizable to children with bilateral congenital cataracts and to children with traumatic cataracts.