

Infant Aphakia Treatment Study (IATS)

Study Protocol

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Chapter 1

Background and Summary

1.1 Objectives

The Infant Aphakia Treatment Study (IATS) is a randomized, controlled multi-center clinical trial with the following objectives:

- To determine whether infants with a unilateral congenital cataract are more likely to develop better vision following cataract extraction surgery if (1) they undergo the primary implantation of an IOL or if (2) they are treated primarily with a contact lens.
- To determine the occurrence of postoperative complications among infants with a unilateral congenital cataract if (1) they undergo the primary implantation of an IOL or if (2) they are treated primarily with a contact lens.
- To determine whether the parents of infants with a unilateral congenital cataract experience less stress if (1) their child is primarily treated with an IOL or if (2) their child is treated primarily with a contact lens.

1.2 Rationale of the Study

The IATS is important for the following reasons:

1. Intraocular lenses (IOLs) are now the accepted treatment after cataract extraction in older children and are being used increasingly in younger children and infants. However, little is known about their safety or the most appropriate power to implant in a rapidly growing eye. Before they supplant contact lenses as the preferred means to optically correct aphakic infants, their safety and efficacy for this age group need to be established.
2. Most of the data addressing the issue of how infants should be corrected optically after removing a unilateral congenital cataract is retrospective and uncontrolled. Most series are highly selective and exclude patients who have failed to return for follow-up examinations. Thus, there is much to be learned regarding the precise estimates of success and the factors associated with favorable and unfavorable outcomes.
3. While contact lenses have been the standard means of optically correcting aphakia in infants, they are associated with a number of problems that limit their effectiveness. These problems include corneal complications such as bacterial keratitis, lens loss, difficulty inserting and removing the lenses in a small child, and difficulty fitting the steep corneas of infants. Adherence with contact lens use is a significant factor in the poor visual outcome in many children with unilateral aphakia.

4. An alternative treatment modality, the implanting of an IOL, has been used by a few surgeons to correct unilateral aphakia during infancy. These surgeons have reported better visual outcomes, but more postoperative complications with the use of IOLs compared to contact lenses.¹⁻⁵ It remains to be determined if the increased incidence of postoperative complications is sufficiently offset by the improved visual outcome.
5. A recent series reported that children corrected with IOLs have a lower incidence of cosmetically significant strabismus than children corrected with contact lenses.⁶ The improved ocular alignment of the patients with IOLs has been ascribed to the constancy of the optical correction they are receiving relative to that received by children corrected by contact lenses alone. However, these series have largely focused on older children with acquired cataracts. It is unknown whether this effect will be observed in infants with congenital cataracts.
6. Inserting and removing a contact lens from a small child's eye can be very stressful for parents, particularly if they are unfamiliar with contact lenses. In addition, many parents do not trust other caregivers to monitor the child's contact lens wear, limiting their childcare options. An IOL could potentially obviate these problems and thereby reduce the stress experienced by the parent of an aphakic child.
7. Regardless of whether the trial determines that one therapeutic approach results in a better visual outcome than the other, the data collected will still provide valuable information regarding the relative risks of surgical complications with these two treatment modalities.

1.3 Synopsis of Study Protocol

Major eligibility criteria:

- Visually significant congenital cataract (≥ 3 mm central opacity) in only one eye
- Age 28 days to <7 months and at least 41 post-conceptual weeks at the time of cataract surgery
- No microcornea (diameter < 9mm), glaucoma, uveitis, retinal and optic nerve disease, prematurity, anterior persistent fetal vasculature (PFV) causing stretching of the ciliary processes or posterior PFV, or ocular disease in the fellow eye

Sample size: 114 patients recruited over 4 years

Treatment groups: Cataract extraction with randomization to one of two treatment regimens for the aphakia: IOL correction or contact lens correction.

Examination Schedule:

- One day, one week, 1 and 3 months following cataract surgery and then every three months until the end of the study (about 4 years).
- Visual acuity assessment at 12 months of age measured by a traveling examiner using Teller Acuity cards.

- Exam under anesthesia at 2-4 weeks prior to the visual acuity assessment at 12 months of age.
- Assessment of parenting stress at 3 months postoperatively and at 15 months of age.
- 48-hour recall diaries will be done at the 1-month and the visual acuity assessment visits. These will be followed approximately one month later by completion of the mailed, 7-day Eye Care Diary. 48-Hour recall interviews will be conducted over the telephone by DCC staff quarterly starting 3 months after surgery.

Primary Outcome: *Difference in grating acuity between all eyes having treatment for cataract and all fellow eyes measured by a traveling examiner using Teller Acuity Cards at 12 months of age.*

Secondary Outcomes: Visual function in the eye with the cataract, ocular complications, parenting stress, compliance with patching and optical correction.

Chapter 2

Screening and Enrollment of Patients

2.1 Eligibility Assessment

All infants less than 7 months of age with a unilateral cataract are potentially eligible for the study. The eligibility and exclusion criteria are listed below. Some of the criteria are assessed during a clinical exam (Section 2.4.2) and other criteria must be evaluated during an examination under anesthesia (EUA) (Section 2.4.3). Patients who meet the criteria that do not require an EUA will be approached to provide informed consent to undergo an EUA and be randomized to either IOL or Contact Lens treatment if the criteria are met. For all patients less than 7 months of age with a unilateral cataract, an Initial Screening Form will be completed which requests patient initials and date of birth, an indication of whether or not the patient met the assessed entry criteria, and the reasons an eligible patient was not enrolled in the study. A HIPAA waiver will be obtained at each clinical center to collect screening data for patients not enrolled.

2.2 Informed Consent and Enrollment

Written informed consent must be obtained from the parent(s) or legal guardian(s) of the infant before performing any procedures that are not part of the patient's routine care. The study will be discussed with the parent(s) or legal guardian(s) of a child who is eligible for participation in the study based on criteria assessed during the initial outpatient examination when the diagnosis of a cataract is confirmed. Parent(s) or legal guardian(s) will be given the informed consent to read. The investigator will review potential benefits and risks of participation in the study and answer any questions. If the parent/legal guardian expresses any reservation about the study, it is best to allow the parent/guardian time to think about the study before proceeding to randomization. The parent or legal guardian must also be willing to defer cataract surgery until the child is at least 28 days of age. Discussion of the study with family members and with the patient's pediatrician should be encouraged.

After informed consent is obtained, the Office Exam Form, which contains patient information and data from the clinical exam, is completed and the child will be scheduled for an EUA to complete the eligibility assessment. If the criteria assessed during the EUA are met, then the patient will be considered enrolled in the study and will be randomized to either IOL or Contact Lens treatment (Section 2.5). The surgeon will immediately perform surgery according to the assigned treatment. If the patient does not meet criteria, the patient will not be enrolled in the study and the surgeon will perform a cataract extraction with the aphakia treated with a contact lens. All IATS investigators have agreed not to perform primary IOL implantation in patients less than 7 months of age with a unilateral cataract outside the study. Whether or not the patient is enrolled, the EUA/Surgery Form is completed which records the results of the surgical procedure.

2.3 Eligibility Criteria

Patients of all races and both genders and independent of socio-economic status will be eligible for the IATS if all of the following findings and conditions are met:

- 1) Age between 28 and 210 days and at least 41 post-conceptual weeks at the time of cataract surgery.
- 2) A visually significant cataract (≥ 3 mm central opacity) in only one eye.
- 3) Informed consent signed by a parent or legal guardian.
- 4) Parent or legal guardian agrees to be contacted by the DCC staff to collect compliance data.

2.3.1 Exclusion Criteria

Patients will be excluded from the IATS if they meet any one of the following criteria:

- 1) The cataract is known to be acquired from trauma or as a side effect of a treatment administered postnatally such as radiation or medical therapy.
- 2) A corneal diameter less than 9 mm measured in the horizontal meridian using calipers.
- 3) An intraocular pressure of 25 mm Hg or greater in the affected eye measured with a Perkins tonometer, tonopen, or pneumotonometer.
- 4) Anterior persistent fetal vasculature (PFV) causing stretching of the ciliary processes or a tractional detachment of the retina.
- 5) Active uveitis or signs suggestive of a previous episode of uveitis such as posterior synechiae or keratic precipitates.
- 6) The child is the product of a pre-term pregnancy (<36 gestational weeks).
- 7) Retinal disease that may limit the visual potential of the eye such as retinopathy of prematurity.
- 8) Previous intraocular surgery.
- 9) Optic nerve disease that may limit the visual potential of the eye.
- 10) The fellow eye has ocular disease that might reduce its visual potential.
- 11) The child has a medical condition known to limit the ability to obtain visual acuity at 12 months or 4 years of age.
- 12) Refusal by the parent or legal guardian to sign an informed consent or to be randomized to one of the two treatment groups.
- 13) Follow-up of the child is not feasible because the child would not be able to return for regular follow-up examinations and the outcome assessments (e.g. transportation difficulties, relocation, etc.).

2.4 Examination Procedures

2.4.1 Patient Information

Patient information to be obtained will include: initials, date of birth, birth hospital, gender, ethnicity, date cataract diagnosed, other congenital abnormalities, referral source, and medical insurance status.

2.4.2 Clinical Testing in Office

Examination procedures include:

1. Ocular motility examination: assess ocular alignment of the eye with the cataract with the Hirschberg, Krimsky or Alternate Prism and Cover Test at near.
2. Presence or absence of nystagmus in the primary position.
3. The direct and consensual pupillary light responses.
4. Pupil diameter of both eyes.

Other procedures which are not requested on the Office Exam Form but which are encouraged include the following:

1. Visual acuity determined by occluding each eye and assessing the child's visual behavior with the other eye.
2. Slit-lamp examination, if possible. If not possible, assess the red reflex with a direct ophthalmoscope before and after dilation.
3. Examination of the retina and optic nerve using indirect ophthalmoscopy of the unaffected and affected eye, if possible.
4. B-scan ultrasonography of the affected eye if the retina and optic nerve cannot be visualized with indirect ophthalmoscopy.

2.4.3 Clinical Testing Under General Anesthesia

After obtaining informed consent from the parent or legal guardian, both eyes are examined under anesthesia for the eligibility and exclusion criteria prior to cataract surgery . The following procedures are performed during this examination:

Thirty (30) minutes prior to the examination-under-anesthesia, both the affected and unaffected eyes should be dilated with one drop of 1% cyclopentolate and one drop of 2.5% neosynephrine. The drops may be repeated on two occasions, every 5 minutes.

The following studies are to be performed during the examination-under-anesthesia.

1. Tonometry, immediately after induction of general anesthesia, using a pneumotonometer, tonopen or Perkins tonometer.
2. Measurement of the horizontal corneal diameter using calipers.
3. Biomicroscopy using a hand-held slit lamp.
4. Keratometry of both eyes - Ideally a handheld autokeratometer should be used to obtain the K readings such as the Alcon Renaissance Hand Held Keratometer, but if this is unavailable a manual keratometer may be used. At least two keratometry measurements should be taken in

both the affected and unaffected eyes to ensure that the results are accurate; the 2 average K readings should be within 1 D of each other. If the two average K readings are more than 1 D different, then make a third measurement and find the average of the two closest K readings.

5. Cycloplegic refraction using retinoscopy of the fellow eye and of the eye with the cataract

6. Examination of the retina and optic nerve using indirect ophthalmoscopy.

7. B-scan ultrasonography if the retina and optic nerve cannot be visualized with indirect ophthalmoscopy.

8. A-scan biometry of both eyes using immersion if possible – take the measurement from the scan with the best wave forms (i.e., highest peaks with a perpendicular retinal spike) or, if applanation biometry is used, the A-scan with the greatest AC depth. The phakic setting on the ultrasound unit should be used when obtaining the axial length measurements. The axial length measurement from the affected eye with the deepest anterior chamber depth and a 90 degree angle between the baseline and the retinal spike should be used for the IOL calculations.

2.5 Specifics of the Patient Randomization Process

For patients who meet the eligibility criteria of the first stage of screening and the parents agree to participate in the study or the decision is pending, the clinical coordinator faxes the Initial Screening Form to the DCC and calls the DCC alerting them that the fax has been sent. DCC staff will fax to the clinical center a Treatment Assignment Envelope Form with the patient's IATS ID, initials, date of birth, scheduled surgery date, patient's age at surgery and the color and letter code of the treatment assignment envelope to use for this patient.

Before the study starts, each center will be given a batch of 52 treatment assignment envelopes. There will be two sets of 26 envelopes each, one set for each of the two age strata (28-48 days old at surgery and 49-210 days old at surgery). The envelopes for the two age strata will have different colors. Each envelope will have a unique code consisting of two letters. One letter indicates the age stratum with 'Y' for the 28-48 days old stratum and 'O' for the 49-210 days old stratum. For each stratum the second letter will identify the specific envelope and will consist of the letters A-Z. Thus, the 28-48 days old stratum envelopes will have letter codes 'YA' – 'YZ' and the 49-210 days old stratum envelopes will have letter codes 'OA' – 'OZ'. **NOTE: The envelopes will not be used in order according to the code on the envelope. For each patient you will receive a Treatment Assignment Envelope Form from the DCC specifying the letter code for the envelope to use.** For example, if your first patient is 95 days old at surgery, the envelope you might be told to use could be "OP".

If surgery is delayed beyond the originally scheduled date, the treatment assignment envelope may no longer be valid. This would happen, for example, if a patient would have been 48 days old or less at the time of the originally schedule surgery but because the surgery is delayed the patient will be older than 48 days at the new surgery date. In this case, the patient would move from the younger age stratum to the older age stratum and the treatment assignment envelope would have to be changed. If this happens, the clinical coordinator will mail the original treatment assignment envelope back to the DCC. Also, the clinical coordinator should modify the Initial Screening Form to indicate the new surgery date and then re-fax the form to the DCC. The DCC will fax a new Treatment Assignment Envelope Form specifying the code for the

treatment assignment envelope to be used for the patient. The Treatment Assignment Envelope Form will also indicate the last date on which surgery could be done for the patient to not exceed the maximum age limit for the study.

At the time of surgery, the clinical coordinator retrieves the treatment assignment envelope with the code indicated on the Treatment Assignment Envelope Form. The treatment assignment envelope will be taken to the EUA along with the IOL Power Table and the yellow instruction sheet listing the EUA and surgical protocol procedures. The treatment assignment envelope will remain sealed until the surgeon has confirmed that the patient is eligible for the study. If the patient meets all the eligibility requirements, the patient is officially enrolled and the treatment assignment envelope can be opened. A card with a peel-off label containing the treatment assignment is removed and the label is placed in the space provided on the EUA/Surgery form. The label will also contain the ID of the treatment assignment envelope. The surgeon then performs the assigned treatment. If the surgeon determines that the patient does not qualify for the study, the treatment assignment envelope remains sealed and the envelope is mailed to the DCC. The surgeon will perform a cataract extraction and the aphakia will be treated with a contact lens.

After the EUA and surgery, whether or not the patient qualifies for the study, the clinical coordinator and surgeon complete the EUA/Surgery Form, which the clinical coordinator faxes to the DCC along with the A-scan tracing from which the axial length was determined.

2.6 Case Report Forms (CRFs)

In this study, data will be collected by having clinical center personnel complete paper CRFs that are faxed to the DCC.

Each center will have a Screening Binder containing:

- 1) Screening Log – A log to track all patients screened at the center.
- 2) Numbered Patient Screening Forms Sections – ID numbered sections containing:
 - A) Initial Screening Form – Blank copies of the Initial Screening Form
 - B) Office Exam Form – Blank copies of the Office Exam Form
 - C) EUA/Surgery Form – Blank copies of the EUA/Surgery Form.

If a patient with a unilateral cataract is screened and found to be ineligible before the EUA, then only the Initial Screening Form is completed and this form is stored in the Screening Binder. If the patient is found to be ineligible at the EUA, the forms listed under A-C above are stored in the Screening Binder. If the patient was randomized, the Initial Screening Form, Informed Consent Form, Office Examination Form, Treatment Assignment Envelope Form and EUA/Surgery Form are moved to a Patient CRF Binder, which has blank copies of the remaining CRFs needed to record the patient's data. Each enrolled patient will have a separate Patient CRF Binder.

The CRFs should be completely filled out, in English, with blue or black ink, on the day of the visit, signed by the PI, faxed to the DCC, and kept in the appropriate section of the Patient CRF Binder. The information recorded on the CRF should accurately reflect the findings of the study visit as recorded in the patient's medical record. Any errors made in recording data on the CRF should be corrected by

- 1) drawing a line through the error,
- 2) writing the correct value next to it, and
- 3) initialing and dating the correction.

The erroneous value should never be obscured by heavy ink, permanent marker, or white-out.

2.7 Patient Contact Information

Adherence with patching and wearing optical correction is an important determinant of success for either treatment. Therefore, concerted effort will be made to measure adherence as described in Chapter 7. Adherence will be measured using both eye-care diaries and phone interviews with the primary caregiver. The diaries will be mailed from the DCC and the phone interviews will be conducted by DCC staff. Therefore, patient contact information must be provided to the DCC. The information requested includes name, home and work addresses, and home and work phone numbers for the mother, father and primary caregiver (if not the mother or father). The form will be kept secure at both the clinical center and the DCC. The information will not be shared with anyone outside the study. The informed consent document includes a description of the information being requested along with a rationale.

Patient contact information should be verified at every visit after Day 1. Any changes should be recorded on the Patient Contact Information Form and kept in the patient's CRF Binder. When changes are made the form should be faxed to the DCC. The DCC will fax back a new version of the Patient Contact Information Form showing the current information.

Chapter 3

Treatment Regimens and Adverse Events

3.1 Treatment Groups

Patients will be randomized to one of the following two treatments:

- 1) Cataract extraction and contact lens (CL) correction.
- 2) Cataract extraction, primary intraocular lens implantation (IOL), plus spectacles, as needed.

3.2 Surgical Protocols

Surgery will be performed only by a certified investigator (see Chapter 8) at an IRB-approved hospital after completion of the randomization procedure using one of the two following protocols. The Acrysof 6mm acrylic IOL (SN60AT, MA60AC) is covered by FDA IDE # G020021.

Thirty (30) minutes prior to surgery, the pupils should be dilated with either cyclogyl (0.5% or 1.0%) and 2.5% neosynephrine or cyclomydril. The drops may be repeated on two occasions, every 5 minutes.

3.2.1 Surgical Protocol for Infants Randomized to Contact Lens Group

- The vitreous-cutting instrument will be used to create a mechanized anterior capsulotomy that is 5 mm or greater in size. The lens nucleus and cortex will be aspirated with the vitreous-cutting instrument.
- The vitreous-cutting instrument will be used to create a posterior capsulotomy that is 4 mm or greater in size. An anterior vitrectomy will be performed through the posterior capsulotomy. All of the vitreous that prolapses into the anterior chamber and about 1/3 of the vitreous in the vitreous chamber should be excised.
- The two limbal stab incisions will each be closed with a 9-0 or 10-0 synthetic absorbable suture.
- One drop of 0.5% or 1% atropine and an antibiotic/steroid ointment will be placed in the operated eye, which will then be patched.

3.2.2 Surgical Protocol for Infants Randomized to IOL Group

- An anterior capsulotomy 5 mm or greater in size will be made either manually with capsulorhexis forceps or in a mechanized manner with a vitreous cutting instrument.
- The lens nucleus and cortex will be aspirated with a vitreous cutting instrument.
- If posterior lentiglobus is present with a pre-existing opening in the posterior capsule or an opening was created iatrogenically during cataract surgery, the posterior capsulotomy should be enlarged to 4 mm and an anterior vitrectomy (cutting speed > 400) should be performed through the limbal incision.

- The wound will be enlarged and the anterior segment filled with a viscoelastic agent. An AcrySof IOL (SN60AT) will be implanted into the capsular bag. If both haptics cannot be implanted into the capsular bag, An MA60 IOL should be implanted into the ciliary sulcus (subtract 1D from the calculated power).
- The scleral tunnel incision will be closed with interrupted 9-0 or 10-0 synthetic absorbable sutures
- The viscoelastic agent will be removed with an irrigation-aspiration instrument
- The infusion cannula will be left in a limbal stab incision.
- A stab incision will be made 1.5 - 2.0 mm posterior to the limbus
- A vitreous cutting instrument will be inserted through this incision site. A central posterior capsulotomy, 4 mm or greater in size, will be created while the anterior chamber is infused with BSS or BSS Plus. About 1/3 of the vitreous immediately behind the IOL will also be excised. The vitreous cutting instrument will then be removed and the stab incision will be closed with a 7-0 or 8-0 synthetic absorbable suture or a 9-0 nylon suture.
- One drop of 0.5% or 1% atropine and an antibiotic-steroid ointment will be placed in the eye and the eye will be patched.

3.2.3 IOL Power Selection

The IOL power will be determined in the operating room based on biometry and keratometry readings. After obtaining keratometry and axial length measurements for both eyes, a look-up table or an IOL calculator based on the Holladay I formula will be used to calculate the IOL power that will provide an 8D undercorrection for infants 4-6 weeks of age and a 6 D undercorrection for infants older than 6 weeks; IOL powers may go up to 40D.

3.3 Postoperative Medical Therapy

For both the IOL Group and the Contact Lens Group, at a minimum, topical prednisolone acetate 1% should be instilled in the pseudophakic eye 4 times a day for 1 month following cataract surgery. If significant inflammation exists in the anterior chamber (2+ or greater) or if there are visually significant precipitates on the optic of the IOL, topical prednisolone acetate 1% can be used more often than 4 times a day and longer than 1 month, but never longer than 6 months. A topical antibiotic should be instilled in the pseudophakic eye 3 to 4 times a day for 1 week following cataract surgery. Finally, atropine 0.5% or 1% should be instilled twice daily in the pseudophakic eye for 2 to 4 weeks following surgery. Medications are instilled in the presence of a contact lens if applicable.

3.4 Occlusion Regimen

An adhesive patch will be worn daily over the phakic eye 1 hour/day per month of age until the child is 8 months old starting the second week following cataract surgery. The unoperated eye will then be patched all hours that the child is awake every other day or one-half the child's waking hours every day. Children should be encouraged to

participate in their normal activities during patching therapy. The occlusion regimen may be modified or discontinued if it is felt to be in the best interest of the child and with the approval of the Steering Committee. ***In the event of patching failure, defined as average daily patching less than 15 minutes in the previous 3 months, the Investigator may initiate a trial of the use of an occlusive contact lens in the normal eye. This also requires the approval of the Steering Committee and is intended as a temporary remedy until the child will accept on-the-face patching.***

3.4.1 Development of Patch Allergy

If an allergy develops to occlusive patches, a cloth patch should be used, which will be provided by the investigator. The cloth patch should be worn over the spectacle lens of the phakic eye. If spectacles are not otherwise needed, plano glasses will be provided by the study for this purpose.

3.5 Contact Lens Correction

3.5.1 Type and Power of the Contact Lens

Patients randomized to the Contact Lens group (aphakic patients) will be fit with a Silsoft or rigid gas permeable (RGP) contact lens shortly after surgery. Initially, the eye will be overcorrected by 2.0 D to provide a near point correction; at two years of age, the eye will be corrected for emmetropia with a contact lens and spectacles with a +3 D bifocal segment for near vision. Parents will be given a spare contact lens to minimize the chance of the child's not having a contact lens to wear at all times. The goal will be to dispense the initial contact lens by the one-week post-operative visit. If an accurate refraction cannot be obtained at that time, a +32 D Silsoft or RGP contact lens should be dispensed. Lens power should then be refined at the earliest opportunity and any parameter changes assessed at each visit. If a Silsoft contact lens cannot be worn successfully, a rigid gas permeable contact lens should be dispensed instead or vice versa. No patients randomized to the IOL group (pseudophakic patients) will be corrected with a contact lens.

3.5.1.1 Fitting Silsoft Contact Lenses

Silsoft is a Bausch & Lomb brand of silicone elastomer contact lenses for the treatment of aphakia. Silsoft lenses are available in five base curves and two diameters. The parameters are:

Base Curve Range

7.5mm (45.00D) to 8.3mm (40.62D) in 0.2-mm steps

<u>Powers (diopters)</u>	<u>Increments (diopters)</u>	<u>Diameters (mm)</u>
+12 to +20	1	11.3, 12.5
+20 to +32	3	11.3

Keratometric (K) readings should be recorded at the time of surgery. The Silsoft lens is fitted on or near the flatter of the two K readings. After selecting the base curve, fluorescein dye may be used with a hand-held slit-lamp or Burton lamp to assess the tear pattern under the contact lens. Since infant corneas are typically small and steep, the 7.5mm base curve lens in the 11.3mm diameter will be used most often. Fluorescein patterns, lens movement and centration should be evaluated at each visit. Retinoscopy will be used to determine the final power.

3.5.1.2 Fitting Rigid Gas Permeable Contact Lenses

Rigid gas permeable contact lenses will be a lenticulated, hybrid aspheric design manufactured in a high DK (92 or greater) material with two edge lift values. Parameter availability is virtually unlimited for base curves, diameters or powers. A diagnostic fitting set and a fitting nomogram has been developed based on the following basic fitting outline:

Base Curve Selection:

Fit 1.0 to 1.5mm steeper than flattest keratometry reading

Diameter Range:

7.8 to 9.5mm; mean=8.5mm

Lens power will be determined by retinoscopy over the diagnostic lens.

Determining RGP Specifications:

All eyes are to be fitted empirically utilizing diagnostic lenses. The diagnostic set of lenses used is based on a formula of base curve radius plus 1.3mm equals the lens diameter. The trial lenses are of high plus powers and lenticulated. The anterior optical zone diameter corresponds to the posterior optical zone size, which equals the base curve radius in millimeters. The anterior optical size is often reduced in size to decrease lens mass. This reduction in mass not only increases the oxygen transmissibility; it significantly influences the physical fit of the lens. However, the anterior optical zone diameter must remain large enough for full pupil coverage in all gazes. The chosen base curve is one that reveals approximately thirty microns of positive tear power (approximately one diopter steeper than central keratometry); fulcrum or “grip” points achieved in the mid-peripheral cornea, adequate edge lift 360 degrees at the lens edge, and a central position. A base curve that exceeds this amount of vault can result in corneal edema due to poor tear film replenishment. The amount of corneal eccentricity in these patients seems to be a factor. The normal adult cornea flattens from the center in a non-linear fashion. This rate of flattening or eccentricity is lower in infant corneas compared to the normal adult cornea. This statement is based solely on the interpretation of fluorescein patterns of RGP lenses on the infant cornea. The amount of axial edge lift of the lens is one of the adjustments that can be made during the fitting and refitting process. The axial edge lift is often increased to loosen the lens on the cornea. With this method of empirical fitting, we are not biased by the central keratometry measurements

performed under anesthesia at the time of surgery. In addition, the central keratometry is not an indicator of the amount of corneal eccentricity.

The diameter of the RGP lens varies with corneal diameter. The diameter of the lens should be large enough to maintain centration and stability. The diameter can be increased without an increase in center thickness by decreasing the anterior optical zone diameter; however, a larger diameter with the same base curve will fit tighter. Lens parameters are adjusted to avoid a center thickness that exceeds 0.50mm, as lens thickness affects the color, gas permeability, and weight of the lens.

Diagnostic Fitting Kits

A diagnostic fitting set will be used to determine lens parameters for each patient. The diagnostic lenses will be manufactured without a UV filter. This will allow the practitioner to better evaluate the fluorescein pattern without the aid of a wratten filter. The diagnostic set will contain lenses with the following parameters:

Diopters/MM	Power	Diameter	Model
45.00 / 7.50	+22.00	8.8	Star C
46.00 / 7.34	+22.00	8.6	Star C
47.00 / 7.18	+24.00	8.4	Star C
48.00 / 7.03	+24.00	8.3	Star C
49.00 / 6.89	+26.00	8.1	Star E
50.00 / 6.75	+30.00	8.0	Star E
52.00 / 6.49	+30.00	7.9	Star E

* Star C has a “looser” axial edge lift value than Star E

3.5.2 Contact Lens Failure and Secondary IOL Implantation

A child will be considered to be a contact lens failure if he or she wears a contact lens for less than 4 hours a day on average over a period of 8 consecutive weeks. Ideally, the child will undergo a trial with both a Silsoft and rigid gas permeable contact lens. As a last resort, a custom soft contact lens may be worn.

Aphakic spectacles may be worn as necessary, for example, between trials with the different types of contact lenses.

Before an IOL implantation is done, the investigator should complete a “Request for Secondary IOL Implantation” form to the DCC. **The approval of the steering committee is required before the secondary IOL implantation is performed.** This approval is required for all patients for the entire duration of the study, including after the patient has had the visual acuity assessment at one year of age.

Unless the best interests of the child are at stake, every effort should be made to delay an IOL implantation in a child assigned to contact lens treatment until after the visual acuity assessment by the traveling examiner is done at approximately 12 months of age. Note

that the time window for the assessment is 10-14 months of age with 11-13 months of age preferred. If the IOL implantation must be done before 10 months of age, then the visual acuity testing center should be consulted to determine if a visual acuity assessment could be done in that particular patient.

Ultimately, we plan to compare the two treatments for aphakia (IOL vs Contact Lens) based on optotype visual acuity measured when the child is 4-5 years of age. Optotype visual acuity is a more definitive measure of visual function. Therefore, it is critical to avoid secondary IOL implantation in patients assigned to the contact lens group until the optotype visual acuity can be done.

IOL for Secondary IOL Implantation: Either PMMA or ACRYSOFT IOLs may be used for secondary IOL implantation. In most cases the IOL should be implanted in the ciliary sulcus after severing all posterior synechiae. If the anterior and posterior capsules can be separated easily and the Soemmerring ring can be aspirated, the IOL can be placed into the capsular bag. If the IOL is placed in the sulcus, the IOL optic should be between 6 and 7 mm in diameter and the overall diameter of the IOL should be between 13 and 14 mm. If the IOL is placed into capsular bag, the optic diameter should be between 5.0 and 6.0 mm with an overall diameter between 12 and 13 mm. Only FDA approved IOLs will be used in the study. The power of the IOL for the secondary IOL implantation is at the discretion of the surgeon.

3.6 Spectacle Correction

3.6.1 Contact Lens Group (Aphakic Patients)

Aphakic Eye

Spectacles will not be initiated in the contact lens group until the children are two years of age, at which time they will be prescribed a "D" segment bifocal lens with a distance correction of emmetropia and near correction of +3 D, except for children who are deemed to be non-compliant with one or more types of contact lenses. An aphakic spectacle correction can be prescribed for these children as needed at any time.

3.6.2 IOL Group (Pseudophakic Patients)

Pseudophakic Eye

Infants randomized to the IOL group will be prescribed spectacles by the one-month post-operative visit if any of the following conditions exist:

- Hyperopia greater than 1 D
- Myopia greater than 3 D
- Astigmatism greater than 1.5 D

Below the age of 2 years, the aim will be to correct the refractive error to -2 D. At age 2 years or older the aim will be to have a distance correction of emmetropia with a near correction of +3 D.

3.6.3 Unoperated Eye for Patients in Both Treatment Groups

The unoperated eye will be corrected with spectacles if one of the following conditions exists:

- Hyperopia > 5 D
- Myopia > 5 D
- Astigmatism > 1.5 D

The aim will be to correct the refractive error to between 0 and +3 D. If the eye does not have a refractive error exceeding the parameters listed above, a plano lens should be prescribed.

3.7 Adherence (See Also Chapter 7)

Adherence with patching and the wearing of the prescribed optical correction will be assessed by a telephone interview conducted by the DCC at a random time at approximately 3-month intervals. In addition, a one-week “eye care diary” will be kept to document adherence and will be completed annually at approximately 2 months after surgery and 1 month after the visual acuity assessment at 12 months of age and then annually at approximately 25, 37, and 49 months of age. A two-day “eye care diary” will be completed by the mother, with assistance from the clinical coordinator, at the 1 month follow-up visit and again at the age 12 months visual assessment visit.

3.8 Adverse Events/Risks

3.8.1 Risks of Lensectomy

A lensectomy is the standard means of removing a cataract in a child. A lensectomy is known to increase the risk of elevated intraocular pressure (glaucoma), retinal detachment, and a misshapen pupil.

3.8.2 Risks of IOL Implantation

Implanting an IOL in an infant's eye increases the risk of membrane formation across the pupil. These eyes are also at increased risk of having lens material reform. In some cases, this material may extend across the pupillary space and interfere with the vision of this eye. In either case, a reoperation may be necessary to remove the proliferating tissue. In some cases the IOL may become dislocated; it may need to be repositioned surgically.

3.8.3 Risks of Contact Lenses

Contact lenses increase the risk of bacterial keratitis particularly when worn on an extended wear basis. In addition, a corneal abrasion may occur at the time of lens insertion or removal.

3.8.4 Risks of Occlusion Therapy

The risks of occlusion therapy are limited to irritation of the skin. Removal of the patch every other day and treating the skin with emollients should be an effective treatment. *Also, Milk of Magnesia may be applied to the skin and allowed to dry before placing the patch.*

3.8.5 Reporting Adverse Events

At each follow-up examination, a check will be made for adverse events. The following events would be considered serious unexpected adverse events: glaucoma, retinal detachment, endophthalmitis, IOL subluxation, persistent corneal edema, bacterial keratitis. The following events would be considered minor and expected after cataract surgery in infants: corneal abrasion, transient corneal edema, wound leak, corectopia, hyphema, IOL capture, pupillary membrane, transient raised IOP, lens re proliferation into the visual axis.

These adverse events or any other serious vision threatening complications are to be noted on an Adverse Event Form that is to be faxed immediately upon completion to the DCC. A similar procedure will be followed if an adverse event is discovered at times other than a regularly scheduled follow-up examination.

3.8.6 Data Safety and Monitoring Committee (DSMC)

An independent DSMC appointed by the National Eye Institute will be responsible for monitoring patient safety and study performance. The DSMC will meet semiannually to review accumulated data and can request interim reports as deemed necessary. The DSMC consists of two pediatric ophthalmologists who are not affiliated with the study, two biostatisticians not affiliated with the study (one of whom will serve as chair), a pediatric vision assessment professional, and *the mother of a child who had bilateral congenital cataracts* serving in the role of patient advocate. An NEI representative will serve as an ex officio member. The two pediatric ophthalmologists on the DSMC will be supplied with monthly reports of adverse events.

3.8.9 Medical Monitor

In addition to the DSMC, an Emory ophthalmologist will serve as medical monitor. This individual serves as a resource for the DCC and will review adverse events on a monthly basis. The medical monitor will alert the Data and Safety Monitoring Committee if he determines, based on clinical judgment, that patient safety is jeopardized.

Chapter 4

Patient Follow-up, Visual Acuity Assessment, and Reoperations

4.1 Follow-up Examination

The follow-up examination schedule approximates standard clinical practice. More frequent examinations may be performed at the discretion of the investigator. This will likely be the case if complications develop during the postoperative period.

4.2 Follow-up Examination Schedule

Follow-up examinations may be performed as frequently as desired by the surgeon during the 3-month interval following cataract surgery. But at a minimum the child should be examined one day, one week, 1, and 3 months following cataract surgery. Thereafter, examinations will be performed by the investigator at 3-month (± 2 weeks) intervals. An examination under anesthesia will be performed 2-4 weeks before the visual acuity assessment at 12 months of age; all other examinations will be performed in the office. Grating acuity estimates using the Teller Acuity Cards will be obtained at age 12 (± 2) months by a trained examiner who will travel to each study site. Each patient will have undergone an EUA two weeks prior to these grating acuity assessments to ensure that the patient is wearing the appropriate optical correction when tested by the traveling examiner. The traveling examiner will not be informed of the clinical status of the patient and will not have participated in the clinical treatment of any of the patients.

4.3 Follow-up Examination Procedures

4.3.1 Routine Examinations

Routine examinations will be performed by the clinical investigator and will include the following:

- Qualitative visual acuity
- Motility assessment by the alternate prism and cover test, Krimsky test, or Hirschberg light reflex test
- Biomicroscopy or pen-light examination of the anterior segment and pupils
- Retinoscopy with hand-held lenses or phoropter
- Indirect ophthalmoscopy of the fundus
- A visit with the contact lens professional for children in the CL arm of the study

4.3.2 EUA at 2-4 Weeks Prior to Visual Acuity Assessment at 12 Months of Age

The following studies are to be performed during the examination-under-anesthesia.

1. Tonometry, immediately after induction of general anesthesia, using a pneumotonometer, tonopen or Perkins tonometer.
2. Measurement of the horizontal corneal diameter using calipers.
3. Biomicroscopy using a hand-held slit lamp.
4. Keratometry of both eyes - Ideally a handheld autokeratometer should be used to obtain the K readings such as the Alcon Renaissance Hand Held Keratometer, but if this is unavailable a manual keratometer may be used. At least two keratometry measurements should be taken in both the affected and unaffected eyes to ensure that the results are accurate; the 2 average K readings should be within 1 D of each other. If the two average K readings are more than 1 D different, then make a third measurement and find the average of the two closest K readings.
5. Refraction using retinoscopy of the operated eye and of the fellow eye (cycloplegic).
6. Examination of the retina and optic nerve using indirect ophthalmoscopy.
7. B-scan ultrasonography if the retina and optic nerve cannot be visualized with indirect ophthalmoscopy.
8. A-scan biometry of both eyes using immersion if possible – take the measurement from the scan with the best wave forms (i.e., highest peaks with a perpendicular retinal spike) or, if applanation biometry is used, the A-scan with the greatest AC depth. Choose the phakic or aphakic setting on the ultrasound unit when obtaining the axial length measurements. The axial length measurement from the affected eye with the deepest anterior chamber depth and a 90 degree angle between the baseline and the retinal spike should be recorded.

4.4 Visual Acuity Assessment (Primary Study Outcome)

A traveling examiner will perform an outcome examination at approximately age 12 months. The target testing age will be 12 months with an acceptable range of 2 months on either side of this target. Ideally, the testing will be conducted within one month of the target age (11-13 months of age). The reason for this stipulation is that monocular testing becomes increasingly difficult after 12 months of age because the infants are less and less tolerant of wearing a patch. Although the infants enrolled in this study are experiencing patching on a routine basis to treat their amblyopia, the testing situation is more stressful and their cooperation cannot be assured. The original testing session should be scheduled within the 2-month time window (11-13 months of age) if at all possible. This will also allow for the possibility of rescheduling and ensure that the testing is still within the stipulated 4-month window (10-14 months of age).

The examiner and the study center coordinator will work closely together to schedule the visual acuity assessment visits at a mutually agreed upon time within the time window. We anticipate good cooperation from the parent(s) in scheduling this visit. They will be aware of the specialized attention their child is receiving from the traveling examiner and will be informed of the importance of this particular assessment.

At clinics where the Teller Acuity Cards are routinely used for clinical purposes, the investigators are advised not to use the cards to evaluate the child's acuity for clinical purposes on the same day as the traveling examiner is collecting data for this study.

The patient will be examined during the EUA 2 to 4 weeks prior to the acuity testing. The purpose of this examination will be to ensure that the patient is wearing the most accurate optical

correction measured at the EUA. It is very likely that the optical correction in these patients will change significantly between the 9- and 12-month examinations. It will be the responsibility of the clinic coordinator to ensure that any required changes in optical correction are in place prior to the acuity testing. The clinic coordinator will assist the parent(s) in obtaining new spectacles or contact lenses as required and assure that these are available and in place before the acuity testing.

4.4.1 Preparation for Outcome Assessment Examination

Because of the time and expense involved with the traveling examiner's visiting clinical sites, it is imperative that the examiner and patient's schedules be carefully coordinated to avoid either's being inconvenienced. The clinic coordinator should contact the Vision Testing Center at least 3 months prior to the time the outcome assessment is to be performed. The Vision Testing Center and the clinic coordinator will agree on several possible dates for the outcome assessment. *It will be necessary to coordinate the acuity testing date with the EUA date, so both appointments need to be scheduled at the same time. Surgical time may be the limiting factor if the schedules are not made well in advance. If for any reason the EUA date needs to be rescheduled (the child is sick, family crisis), the coordinator will need to work carefully with the Parent/Caregiver as well as the Vision Testing Center to coordinate alternate dates. The Acuity Test Date should be agreed upon between the Clinical Center and the Vision Testing Center prior to determining the EUA date.* The clinic coordinator will then contact the parent(s) of the child to be tested and determine which date would be best for that patient. After confirming this date, the Vision Testing Center will be notified of the date for the examination. One month prior to the appointment, the clinic coordinator will send a reminder to the patient in the mail. In addition, information will be included in this mail giving detailed instructions as to what will happen at the appointment and what needs to be done to prepare for the appointment. One week before the appointment, the clinic coordinator will call the parent(s) of the child to confirm the appointment. Finally, early on the day before the outcome appointment, the clinic coordinator will again call the parent(s) of the patient to confirm the appointment. *It will also be important for the local site PI to contact the Parent/Caregiver by phone to remind them of the acuity testing visit. This personal contact is intended to stress the importance of this particular visit to the Parent/Caregiver and to assure their attendance.* If the parent(s) indicate after either of these telephone calls that they will not be able to keep the appointment, the clinic coordinator will immediately notify the Vision Testing Center so the traveling examiner can modify his or her travel plans.

The patient will have been examined two *to four* weeks prior to the acuity testing date, as stated above, to ensure proper refractive correction. The clinic coordinator will assist the parent(s) in obtaining new spectacles and/or contact lenses prior to the acuity testing as needed. The parent(s) will be called the night before the examination to remind him/her of their appointment.

4.4.2 Protocol for Resolution Acuity Testing Using the Teller Acuity Cards

General

Prior to the traveling examiner's meeting the patient, the clinical investigator or clinical coordinator will check to be sure the child is wearing the optical correction prescribed and

completes the Teller Acuity Card Assessment – Site Coordinator Form. The traveling examiner does not review the patient's chart prior to conducting the visual acuity assessment.

Conduct of Grating Acuity (Teller Acuity Card) Assessment at 12 Months of Age

Monocular grating acuity will be assessed by the traveling examiner with the Teller Acuity Cards. The examiner will bring a complete set of Vistech Teller Acuity Cards to the study center. Dr. Hartmann will accompany the traveling examiner on the initial visit to each site. She will be responsible for assuring that all testing conditions are satisfied. She will work directly with the site clinical coordinator prior to this initial visit and review the requirements for the physical set-up for the grating acuity testing. Sufficient time will be allocated at the initial visit to review the location of the testing within the clinic and to assure that all protocol requirements are being met. For example, if lighting is inadequate, the clinical coordinator will assist Dr. Hartmann in obtaining the necessary extra devices needed for indirect illumination in the testing room.

Lighting Conditions for the Grating Acuity Testing

Room lighting is usually sufficient to provide a luminance of the screen of at least 10 cd (candela) /m² . This luminance will be verified by the traveling examiner at the time of the testing. The traveling tester will bring a luminance meter for this purpose. Dr. Hartmann will supply the luminance meter for the study from her laboratory equipment. Luminance must be uniform across the screen and the acuity cards, so that shadows do not distract the child's attention from the test gratings. When the existing lighting does not meet these conditions, additional lights will be used and are directed toward the ceiling of the room to provide indirect illumination of the screen and cards.

Location of Grating Acuity Assessments

Testing is conducted in a space that is at least 6' X 6' and is as free as possible from distracting objects or noises. A portable screen that allows horizontal card presentation is used to block out any remaining distractions in the room. This screen may be either a table-top model as manufactured by Vistech (for those clinical centers who already own the screen) or a free-standing model designed at the Vision Testing Center and shipped to the clinical site. At this age the child will be seated in the parent's lap for the testing. The adult will be screened from the card using a shield placed at the adult's eye level, to avoid assisting the child in a response.

Order of Testing of Eyes

The aphakic or pseudophakic eye will be tested first so that in case the infant becomes uncooperative during the test, the affected eye will have a measurement. Every effort will be made to test both eyes, including taking a break, even to the extent of postponing the test until the next day.

Patching

Parents will be instructed to have the child wear the patch to the visual acuity assessment to avoid the child becoming uncooperative at the exam when the patch is first put on. The visual acuity examiner will inspect the patch to insure that it is properly positioned. A Coverlet patch will be used as an occluder and the traveling examiner will be responsible for having a supply of these patches. The patch will be used for all children except those with nystagmus. Children

with nystagmus should have the eye that is not being tested covered with a high plus lens, e.g. +10 D.

Test Distance

The standard test distance for 12-month-old infants is 55 cm, measured from the screen to the child's eyes. Children with poor visual acuity may require testing at a nearer distance. Recommended choices for nearer distances are 38 cm (the distance used with infants younger than 6 months), 19 cm, and 9.5 cm. Use of 19 cm or 9.5 cm allows easy calculation of acuity scores. At 19 cm, the acuity value is one-half that listed in the Vistech Teller Acuity Card manual for 38 cm (e.g., a score of 6.5 cycles/cm provides an acuity estimate of 4.9 cycles/degree at 38 cm and an acuity estimate of 2.45 cycles/degree at 19 cm). Similarly, an acuity value obtained at 9.5 cm is one-quarter that listed in the Vistech manual for 38 cm (e.g., a score of 6.5 cycles/cm at 9.5 cm indicates an acuity estimate of 1.23 cycles/degree).

Test Duration

For most 12-month-old infants Teller Acuity Card testing requires less than 5 minutes per eye. Infants with severely impaired vision may require as much as 10 to 15 minutes per eye.

Recording Results

Data Form

The examiner records grating acuity results on a data sheet identified as the Teller Acuity Card Assessment Form. The original of this form is retained by the traveling examiner and stored at the Visual Acuity Testing Center. A copy is faxed to the DCC from the clinical site after the completion of the exam. This form is not left at the Clinical Center or retained in the patient's binder.

4.4.3 Resolution Acuity Testing Procedure (Teller Acuity Cards)

Usual Testing Method for Using the Teller Acuity Cards

- Start with two stacks of cards
- On the top of one stack is the 1.3 cycles/cm card. Beneath this card are acuity cards containing higher spatial frequencies (narrower stripes) arranged sequentially from low to high spatial frequency
- The second stack contains spatial frequencies lower than 1.3 cycles/cm (wider stripes) arranged sequentially from high to low spatial frequency (smaller to larger stripes).
- This provides a continuous series of gratings in the two stacks. Therefore, in order to proceed sequentially to higher or lower spatial frequency gratings, the observer has only to move the top card in one stack to the top of the other stack and pick up the next card in the first stack.

- Check the lighting of the cards with the light meter that is provided with the Teller Acuity Cards or a luminance meter. It is sometimes difficult to get 10 cd/m² or greater under normal office lighting and additional lights should be added.
- If supplemental lights are needed, use indirect sources (e.g., directed toward the ceiling), in order to avoid casting uneven shadows on the cards.
- Seat child (on the parent's lap) 55 cm from cards
- Testing Procedure
 - A. Testing begins with the 1.3 cycles/cm card
 - B. During the testing the examiner uses his or her face or a toy to attract the child's attention to the opening in the screen. Initially, the examiner shows the child the 1.3 cycles/cm card. The grating on this card is easily detected by normal children 12 months of age and older. After the child responds to the card, the examiner rotates the card by 180 degrees, to position the acuity grating on the opposite side of the card (left versus right). The examiner does not look at the card between presentations and does not know the exact location of the stripes. The examiner has made a guess as to the location of the stripes based on the child's fixation response to the initial presentation and anticipates that the child will look at the opposite side of the card once it is rotated 180 degrees. The examiner again places the card up to the opening in the screen and watches the child's response. Typically, the child's eye movements will indicate clearly that the child can detect the grating. That is, the child will show clear fixation of one side of the card upon the first presentation, and after the card has been rotated the child will show clear fixation of the opposite side of the card.
 - C. If the examiner judges that the child can see the grating, the examiner is permitted to look at the front of the card to confirm that the grating is actually on the side to which the child responded. After the child has shown a clear response to the 1.3 cycles/cm grating, and the examiner has confirmed the accuracy of his/her judgment, the examiner proceeds to show the child cards containing sequentially higher spatial frequency gratings until no response is obtained from two successive gratings. Acuity threshold is estimated as the highest spatial frequency grating (narrowest stripe width) to which the child shows a clear response.
 - D. During sequential presentation of the cards, the examiner is required to show each acuity card to the child at least twice, once with the grating in each of the two possible test locations (left and right) before making a decision as to whether the child can see the grating. With low spatial frequencies (wide stripes), the child's response is usually so clear that only these two presentations are required. As the stripes on the cards approach and go below the child's acuity threshold, it is often

necessary for the examiner to present a card more than two times to reach a decision concerning whether or not the child is responding to the grating. **IT IS ESPECIALLY IMPORTANT WHEN PRESENTING GRATINGS NEAR THRESHOLD THAT THE EXAMINER REMAIN MASKED TO THE LOCATION OF THE GRATING SO THAT HIS OR HER JUDGMENT IS BASED SOLELY ON THE CHILD'S RESPONSE.** The examiner must be careful to make a decision concerning whether or not the child can see the grating before looking at the front of the card to determine actual grating location. The examiner can postpone making a decision about the child's response and present an easy card at any point in the testing to ensure that the child is continuing to cooperate with the testing and to reassure both herself and the child that there is something to look at on the cards. In other words, an important feature of the procedure is that the examiner is not required to show the cards in strict sequential order. As threshold is approached, a child will often become bored, distracted, or fussy. When this happens, it is helpful to return to a low spatial frequency grating (wide stripes) to which the child showed a clear response earlier in testing. Another clear response to this low spatial frequency grating is a good indicator that the child's reaction to the higher spatial frequency grating was related to his or her inability to see the grating, not to a general lack of attention. The examiner's judgment is always whether or not the child can see the grating pattern (Yes or No). This is a subjective judgment that is highly accurate in a well-trained examiner. It is NOT based on the number of "correct" fixations per se, but rather an overall gestalt judgment on the part of the examiner.

- E. The examiner is required to go back and retest the "threshold" Teller Acuity Card after determining that the child cannot detect the next smaller grating. If the examiner is not convinced that the child resolves the originally specified "threshold" grating, the examiner is required to go back another grating and confirm that the child can see that grating. If the examiner is not convinced that the grating initially thought of as "threshold" can be discriminated by the child, then s/he is required to find the grating that **is** the threshold.
- F. When the examiner is satisfied that he or she has found the boundary between spatial frequencies seen by the child and spatial frequencies not seen by the child, the test is ended and the examiner records the child's acuity as the highest spatial frequency (narrowest stripe width) that he or she judged that the child could see.

Testing Children with Very Poor Acuity

Children with poor acuity will not respond to the 1.3 cycles/cm grating. If this happens, the examiner uses the second stack of cards, i.e., the cards with the lower spatial frequency gratings (wider strip widths). The examiner begins with the lowest or one of the lowest spatial frequency gratings in this stack and then proceeds to higher spatial frequency gratings until he or she judges that acuity threshold has been reached. If no response to any of the standard acuity cards is

obtained at the 55 cm test distance, the examiner will test at 38 cm. If no response to any of the standard acuity cards is obtained at the 38 cm test distance, the examiner will test at 19 cm.

Some children may not respond to any of the acuity cards when they are presented behind the screen, even when the child is moved up to 38 cm. If this happens, the examiner should try testing the child without the screen. To test without the screen, the examiner sits in front of the child, carefully measures the test distance, and then shows the child various cards until an estimate of acuity can be made. Initially, the examiner tries a test distance of 55 cm. If no response is obtained, the examiner moves in to 38 cm. If no response is obtained at 38 cm, the examiner will try the test at 19 cm. If no response is obtained at 19 cm, the examiner will try the test at 9.5 cm. At 19 and 9.5 cm, examiners often find it easier to observe the child over the top of the card rather than through the peephole.

When testing without the screen, the examiner can position the card so that children who fixate with some part of the retina other than the fovea can see the card. If a child has a horizontal nystagmus, the examiner can hold the cards vertically, since it may be easier to distinguish differential fixation of up versus down than left versus right in these children.

Children who fail to respond to any of the standard acuity cards without the stage at 55, 38, 19, or 9.5 cm should be tested with the Low Vision Acuity Card. This card contains a large (24 X 24 cm) patch of very wide stripes (2.2 cm/stripe) and is used to assess the presence versus absence of pattern vision in these children. It is typically used without the stage. The Low Vision card should be presented initially at 19 cm. If the child responds to this pattern, the examiner can retest the child at farther distances, e.g., 38 cm and 55 cm. The final data recording will indicate detection of the Low Vision card at the furthest distance.

It is permissible to move the Low Vision Card and watch for a tracking response. However, other Teller Acuity Cards should be kept stationary when they are presented.

4.4.5 Assignment of Visual Acuity for Patients Whose Vision is Below the Level That Can Be Measured.

We are proposing to use any of four testing distances. We will initiate the testing at 55 cm. If the infant cannot respond to the start card at this test distance as well as the largest stripe width, we will move to the closer testing distance of 38 cm. If the infant still does not respond to the card with the largest stripe at this distance, we will move to 19 cm, and finally 9.5 cm. When we test at the closer distances of 19 and 9.5 cm it is likely that we will be testing away from the Acuity Card Stage. At the test distance of 9.5 cm, the largest stripe width of 0.32 cy/cm yields a Snellen equivalence of 20/6400 (2.5052 logMAR). We will not use the Low Vision Card under any circumstances to provide a numerical estimate of visual acuity. If the infant does not respond to the largest stripe at the shortest distance and we are unable to generate a numerical acuity estimate in the standard manner (clinical method of adjustment), we will assign an acuity of 20/8860 (2.6464 logMAR). This corresponds to a 0.1412 logMAR decrease below 20/6400. The interval 0.1412 is the mean of the intervals between the 20/910 (1.6580 logMAR) and the 20/6400 acuities of the Teller acuity cards at the 9.5 cm distance. Additional information that the

tester will consider when assigning this low level of acuity will include the observed behavior of the child relative to visual tasks, the qualitative visual assessment of the IATS physician, and the parent's description of the child's behavior relative to visual tasks.

Distinguishing Between LP and NLP When There is No Pattern Vision

Children who do not demonstrate any gross pattern vision using even the Low Vision Card will be evaluated for the presence of light perception (LP). If the child does not respond to this assessment, the vision in that eye will be classified as no light perception (NLP).

LP will be tested with a pen light, a Finoff light, or an indirect ophthalmoscope. Testing for LP must take place in a darkened room. If using a pen light, which may not be very bright, the room needs to be totally dark. If using a Finoff light or indirect ophthalmoscope, both of which have bright lights, total darkness may not be necessary but it is still the ideal.

It is necessary to block all light from the eye not being tested for assessment of LP. It will be necessary to use an eye patch as well as having the tester (or parent or helper) place the palm of one hand gently but firmly over the eye patch occluding the eye not being tested. The light should then be presented to the uncovered eye several times, from the front and from the sides. The tester should watch for a consistent change in behavior that occurs only when the light is being presented, (e.g., eye movement towards or away from the light, head turn towards or away, or possibly just a quieting of behavior). If the child does not demonstrate a consistent response to this presentation, the vision in that eye will be considered NLP.

Data Values for Low Vision, LP and NLP

We originally proposed the following method for assigning a logMAR value for patients who fail to recognize the Teller acuity card with the largest stripe:

If the infant does not respond to the largest stripe at the shortest distance and we are unable to generate a numerical acuity estimate in the standard manner (clinical method of adjustment), we will assign an acuity of 20/8860 (-2.6464 logMAR). This corresponds to a 0.1412 logMAR decrease below 20/6400. The interval 0.1412 is the mean of the intervals between the 20/910 (1.6580 logMAR) and the 20/6400 acuities of the Teller acuity cards at the 9.5 cm distance.

We now recognize that this method does not provide a distinction between some pattern recognition, LP and NLP. We propose to assign -2.6464 logMAR for some pattern recognition detected with the Low Vision card, -2.7876 logMAR for LP, and -2.9288 logMAR for NLP. The values for LP and NLP were determined using the 0.1412 logMAR value described above.

4.4.6 Discontinuation of Contact Lens Prior to Traveling Examiner Examinations

If a child randomized to CL correction discontinues CL use prior to the 12 month assessment and has not received a secondary IOL, then the child will wear his aphakic correction in trial spectacles for the examination by the traveling examiner.

4.4.7 Discontinuation of Spectacles Prior to Outcome Examinations

If a child in either the CL or IOL group discontinues the use of the glasses prescribed prior to the outcome examination at 12 months, the glasses prescribed or the same prescription in trial frames will be worn during the grating acuity assessment using the Teller Acuity Cards.

4.4.8 Rescheduling Examinations When the Child is Uncooperative

We will schedule up to three sessions to assess visual acuity for a child. If the child is uncooperative for the first session, we will endeavor to schedule a second session on the same day after the infant has had a lengthy break (several hours). If necessary, the second session will be scheduled for the following day. If the second testing session is unsuccessful, we will request that the parent return at a later date for the third session. We will not attempt three testing sessions on the same trip. If the second session is on the same day, the third session will not be on the following day. The third testing session will be scheduled at least one week after the original testing session. If only one eye is to be tested at the third session (because the other eye was successfully tested at the first or second session), then the third session will be scheduled within 4 weeks of the original testing session. If necessary, Dr. Hartmann will accompany the traveling tester to the third testing session, or possibly come by herself to conduct the testing. Dr. Hartmann will make this decision in conjunction with the traveling tester and the site coordinator. The site coordinator will be asked for an assessment of the need for a different tester and an opinion of the parent's impression of the testing situation.

4.4.9 Rescheduling Missed Examinations

If a patient misses a study visit, the clinical coordinator should call the parent or legal guardian of the patient the same day in an attempt to ascertain the reason for non-attendance for the examination. If the parent/legal guardian can be reached, the clinic coordinator should reschedule the appointment as soon as possible, however, every effort should be made to accommodate the schedule of the parent. If the clinic coordinator cannot reach the parent after three telephone calls at three different times of day on three different days over the course of no more than one week at the primary telephone number, other ancillary telephone numbers listed for the child should be used.

4.4.10 Providing Physicians and Parents the Visual Acuity Assessment Results

The visual acuity test result will be communicated on a form to the physician on the day of the exam along with a graph or table showing normative data by age. The physician can then discuss the results of the test with the parents/caregivers.

4.5 Reoperations

4.5.1 Post-Operative Complications

Potential complications related to the cataract surgery, both in the IOL group and in the aphakic group will be monitored. The time of recognition of the complication, the treatment of the complication, and the results of treatment will be recorded and analyzed.

Reoperations by the investigator will be permitted during the immediate post-operative period for any of the following complications:

1. **Wound leak** - A shallow or flat anterior chamber secondary to a wound leak that is judged by the examiner as unlikely to undergo closure without surgical intervention. Any wound leak persisting for 48 hours will be surgically repaired.
2. **Poor IOL position** - IOLs that are poorly positioned will be surgically repositioned under the following conditions: (1) the optic is subluxed out of the visual axis; (2) the edge of the optic bisects the visual axis; (3) the haptic is displaced into the vitreous or into the anterior chamber; (4) there is severe iris chafing; or (5) there is optic capture by the pupil. If trauma is responsible for the poor IOL position this will be recorded.
3. **Retained lens cortex** - Surgical removal of residual lens cortex will be performed if residual cortical material is felt to be responsible for excessive postoperative inflammation (4+) that persists for 10 days despite the usual postoperative steroid regimen. In the late post-operative period surgery will be performed for any proliferation of cortical material that blocks the visual axis.
4. **Hyphema** - Surgery will be performed for a hyphema under the following conditions: (1) the hyphema is present for 3 weeks; (2) the hyphema occupies more than 50% of the anterior chamber volume and glaucoma is present or (3) the intraocular pressure is elevated to greater than 35 mmHg for more than 72 hours despite maximal medical therapy.
5. **Endophthalmitis** - Vitreous culture and intravitreal antibiotic treatment will be initiated for suspected endophthalmitis. The results of vitreous cultures and gram stains will be recorded.
6. **Retinal detachment** - The choice of surgical procedure for retinal detachment will be left to the discretion of the treating vitreo-retinal surgeon.

7. **Pupillary Membrane** - Surgery to remove secondary membranes or vitreous opacities will be performed if the presence of the opacity is consistent with a decrease in the visual acuity potential to the 20/50 level in the judgement of the examiner.
8. **Glaucoma** - The indication for glaucoma surgery is a sustained intraocular pressure (IOP) of 25 mmHg or greater while receiving maximal medical therapy including a β -blocker, Xalatan, and Trusopt, and persisting for more than two weeks after the discontinuation of topical steroids. Systemic carbonic anhydrase inhibitors are not to be used for more than two weeks and Alphagan and Iopidine are to be avoided. In addition, intraocular pressure above 21 mmHg with ANY of the following: visible and/or measurable enlargement of the cornea compared with the normal fellow eye, asymmetrical progressive myopic shift in the presence of corneal enlargement, and increased optic nerve cup-to-disc ratio of at least 0.2. The choice of surgical procedure will be left to the discretion of the treating surgeon.
9. **Miosis or Corectopia** – A pupilloplasty will be performed if inadequate pupillary dilation precludes the performance of both an accurate refraction and an examination of the optic disc and fundus or if the pupil is so eccentric it is believed that it will compromise the visual acuity of the eye

4.5.2 Strabismus Surgery

Strabismus surgery will be treated with commonly accepted medical practices and will be performed when indicated. The treatment algorithm will be left to the discretion of the Investigator.

Chapter 5

Statistical Considerations

5.1 Sample Size Estimate

The primary hypothesis to be tested in the IATS study is that the mean visual acuity for affected eyes at 12 months of age will be better for children that have an IOL implanted (pseudophakic group) than for children that do not have an IOL implanted and are treated primarily with a contact lens (aphakic group). To test this hypothesis, infants 28 to 210 days of age with a unilateral congenital cataract will be randomly assigned to one of the two treatments and visual acuity will be tested using Teller Acuity Cards at approximately 12 months of age.

IATS investigators conducted a pilot study on a convenience sample of 25 children at 5 clinical centers who had a monocular congenital cataract treated with an IOL or contact lens. A trained visual acuity examiner was sent to each of the 5 centers to standardize the visual acuity testing. The average age at the time of cataract surgery was 10 weeks (range = 2-23) and the average age at the time of the visual acuity exam was 19 months (range = 7-30). The mean \pm standard deviation of the visual acuity (logMAR) in the affected eyes was 0.704 ± 0.318 for the pseudophakic group and 0.873 ± 0.312 for the aphakic group.

The sample size estimate was made to detect a .2 logMAR difference (2 lines of Snellen visual acuity) between the mean visual acuity of the two groups. An estimate of the variance of the visual acuity was calculated from the pilot data above by pooling the observed variances of the two groups using the formula $((n_1 - 1)s_1^2 + (n_2 - 1)s_2^2)/(n_1 + n_2 - 2)$. The decision to pool was based on the similarity of the observed variances of the two groups as verified by an F-test ($p = .97$). The pooled estimate of the standard deviation of the visual acuity was 0.315 logMAR. Rather than use this estimate in the sample size calculation, to be conservative we elected to use the standard deviation based on the upper one-sided 80% confidence limit for the variance. This limit is obtained from the formula $(df \times s^2 / \chi^2_{df, \alpha})$ where df is the degrees of freedom for the estimate of the variance and $\chi^2_{df, \alpha}$ is the value from a chi-square distribution with df degrees of freedom corresponding to a probability of α . (If X is a chi-square random variable with df degrees of freedom, then $\text{Probability}(X < \chi^2_{df, \alpha}) = \alpha$). In this case $df = 23$ and $\chi^2_{23, .2} = 17.19$. The estimate for the standard deviation of the visual acuity in the affected eye that was used in the sample size calculations was .365 logMAR. The interpretation of this estimate is that we are 80% confident that the true standard deviation of the visual acuity in the affected eye is less than .365 logMAR.

The sample size estimate was based on the t test for comparing the means of independent groups. The difference in the means was set at .2 logMAR, the standard deviation was set at .365 for both groups, the Type I error was set at .05, the power was set at .8, a two-tailed alternative hypothesis was used and the standard deviations were assumed to be unknown and unequal. The resulting sample size estimate was 54 patients per group. As a final adjustment, we assumed that 5% of patients would be lost to follow-up before 1 year. This resulted in a sample size estimate of 57 patients per group for a total of 114 patients.

5.2 Stratification

The treatment in this study involves a complex surgical procedure; therefore, surgical skill and technique could possibly have an effect on the outcome. Also, the age of the child at the time of cataract surgery is thought to be an important factor for the visual acuity outcome with younger children having a better prognosis.

Since some centers may have a relatively small number of patients, rather than stratifying by individual center, the centers will be categorized into 3 groups and the randomization will be stratified with the 3 groups. The 3 groups are: (1) Steering Committee Members: Emory U, Indiana U, Duke U, MUSC; (2) Other centers that participated in a randomized pilot study: U of Minn, Vanderbilt U, Dallas, Oregon U; (3) Remaining centers: USC, Harvard U, Miami, Cleveland Clinic, Baylor U. In addition, patients will be stratified according to age with two age groups, 28-48 days and 49-210 days.

5.3 Statistical Power for Other Outcomes

5.3.1 Interocular Difference in Visual Acuity

A secondary analysis will be a comparison of the mean interocular difference in visual acuity at one year of age between the treatment groups. The interocular difference in visual acuity is an assessment of the difference in visual acuity between the affected and unaffected eyes of each patient.

In the retrospective pilot study, the mean (sd) of the interocular difference in visual acuity (logMAR) was 0.260 (0.295) for the IOL group and 0.501 (0.279) for the Contact Lens group. A point estimate for the standard deviation, based on pooling the data for the two groups, was 0.290 and the upper 80% confidence limit is 0.330.

With 0.330 for the standard deviation and with 54 patients per treatment group, the power of the study is 0.88 to detect a 0.2 logMAR difference between the groups based on a two-sided t test for comparing the means of independent groups with probability of a Type I error = 0.05.

5.3.2 Ocular Complications

The power for comparing the percent of patients who experience a complication (such as strabismus) was determined by setting the difference between the two groups and then calculating the percentages that would be symmetrical around 50%. This was done because for a specific sample size the power will be the smallest when the percentages are symmetrical about 50%. Thus the power estimates are conservative. The power was calculated using a z-test for comparing percentages with 54 patients per group and with the Type I error set at .05. For an absolute difference of 20% (for example, 40% vs 60%) the power was .47. For absolute difference of 27%, the power was 0.81. Therefore the study will have power of at least .8 for detecting differences between the groups for the percentages of patients who experience

complications if the percentages differ by 27% or more. In terms of estimation rather than hypothesis testing, with 54 patients in each of the groups, the width of the 95% confidence interval for estimating the percentage of complications varies from $\pm 8\%$ to $\pm 13\%$ as the observed percentage varies from 10% to 50%. The confidence interval calculations were done using the normal approximation to the binomial distribution.

5.3.3 Parenting Stress

A parenting stress assessment (the Parenting Stress Index and a disease-specific measure, the Ocular Treatment Index) will be administered to parents at the 3-month follow-up visit and at the first 3-monthly visit after the visual acuity assessment. Thus, the primary analyses will be a comparison of the mean scores of the two treatment groups 3-months after surgery and when the child is approximately 15 months of age. The statistical power of this comparison was determined using the summary statistics from the Parenting Stress Pilot Study. The mean \pm standard deviation of the child domain scores were: Pseudophakic Group (99.2 ± 16.6), Aphakic Group (110.5 ± 25.9). The sample size was 13 parents in each of the groups. Power was calculated using the independent groups t-test with 54 parents per group, alpha set to .05, the standard deviations set to 16.6 and 25.9, and a two-tail alternate hypothesis. Power was determined for differences in the means of the groups based on a percent difference from the mean score of the Aphakic Group. For example, the power to detect that the mean child domain score of the Pseudophakic Group will be 10% less than the mean of the Aphakic Group, an absolute difference of 11.1, is 0.75. For a 15% relative difference, the power is 0.98. There appears to be adequate power to detect reasonable differences between the means of the two groups. However, there are limitations in the estimates provided by the pilot study. In addition to the small sample size, the pilot study included patients with diagnoses other than unilateral congenital cataract. Also, there was a wide age range among the patients at the time of the test (5 months to 5 years).

5.4 Statistical Analysis

5.4.1 Visual Acuity in the Affected Eye

The primary analysis will be a comparison of the treatment groups based on the mean visual acuity in the affected eye at 12 months of age. The comparison will be made using an independent groups t test. Also, 95% confidence intervals will be computed for the mean visual acuity in each group and for the difference in the means. If the data indicate that a parametric test is not appropriate then a non-parametric test will be done. The analysis will be done following the intention to treat principle. That is, the patients will be grouped according to the treatment to which they were originally assigned.

5.4.2 Interocular Difference in Visual Acuity

A secondary analysis will be a comparison of the treatment groups based on the mean interocular difference in visual acuity between the affected and unaffected eyes of patients at 12 months of

age. The same methods will be used as described for the primary analysis of the visual acuity in the affected eyes.

5.4.3 Ocular Complications

An analysis will be done to compare the percentage of patients in each treatment group with a vision threatening complication. The comparison will be made using a z test. Also, 95% confidence intervals will be computed for the percentage in each group and for the difference in the percentages. If it is determined that the approximate test is not appropriate, then an exact test will be done (Fisher's Exact Test).

5.4.4 Parental Stress

The Primary Caregiver (defined as the person in the family who provides most of the childcare.) will complete both the PSI and the Ocular Treatment Index (OTI) at 3 months after surgery and at the first 3-monthly visit after the visual acuity assessment at 12 months of age (i.e., when the child is approximately 15 months of age). The purpose for collecting these data is to determine if caregivers whose children were assigned to receive a primary IOL report less stress than caregivers whose children were randomized to receive the contact lens. Repeated measures ANOVA will be used to analyze these data. The specific questions to be investigated are: 1) Are the mean PSI and/or OTI scores at 3months after surgery different in the two treatment groups? 2) Are the mean PSI and/or OTI scores when the child is approximately 15 months of age different in the two treatment groups? 3) Within each treatment group are there significant changes in parenting stress from 3-months post-surgery to when the child is approximately 15 months of age? 4) Are the mean changes in parenting stress from 3 months to when the child is approximately 15 months of age different in the two treatment groups?

5.4.5 Analyses For Patching Adherence and Other Covariates

In addition to the analyses on the major outcome variables, other analyses will be done to assess the effect of various covariates on the outcomes. These covariate analyses will be viewed with caution since the sample size for the study was not determined based on these analyses. However, relevant information may be identified by these analyses. The most important covariate of interest is adherence with the patching regimen. We expect that patients who are more adherent with the patching regimen will have a more successful visual acuity outcome. Adherence will be measured three ways: 1) parents will complete a 48-hour recall diary at the 1-month follow-up visit and at the 12-month visual assessment visit, 2) parents will keep a one-week patching diary annually (starting at 2-months post-surgery); 3) an interviewer will call the parents four times each year and collect a 48 hour recall of the patching. These data will be used to construct a measure of adherence. The measure will likely be a weighted average of these different sources of information. Measures will be constructed based on different perspectives: the age of the child, the time point after surgery and a cumulative measure of adherence. The adherence measures will not be constructed based upon the association with the outcome.

Within each treatment group the association between adherence and the visual acuity outcome will be assessed. The specific technique used for the analysis will depend on the coding scales for visual acuity and adherence. The methods likely to be used are chi-square tests, logistic regression, analysis of variance and linear regression.

The level of adherence with the patching regimen will be compared between the two treatments. Again, the specific techniques used will depend on the coding for adherence. Chi-square techniques will be used if adherence is coded as a categorical variable and analysis of variance will be used if adherence is coded as a continuous variable.

To assess the effect of adherence on the comparison of the treatments, the analyses described above for the major outcomes will be done with patients stratified according to an assessment of whether they did or did not comply with the patching regimen. Other techniques that will be used to compare the two treatment groups adjusting for adherence are analysis of covariance (for the outcomes interocular difference in visual acuity and parental stress) and logistic regression (for the presence of vision threatening complications). Clearly, the investigation of the effect of adherence will be painstaking. In all these analyses, the emphasis will be on estimation rather than hypothesis testing.

Adherence with the optical correction regimen will also be measured. We will examine the same questions as described above for adherence with patching. In addition, we will use multivariate statistical models such as logistic regression, analysis of variance, and linear regression to evaluate the combined effect of adherence with both patching and optical correction regimens. Other covariates will be evaluated using similar techniques.

5.5 Interim Monitoring and Analyses

At six-month intervals, interim study results will be presented to an external Data and Safety Monitoring Committee appointed by the National Eye Institute and composed of experienced investigators not participating in the study. This committee will evaluate study performance and patient safety. We are not proposing the use of interim stopping rules based on the primary outcome, visual acuity at 12 months of age, since this assessment will be based on grating acuity and we do not think that the study should be stopped for efficacy reasons using grating acuity. Optotype acuity is a more definitive visual acuity test but it cannot be performed consistently until at least 3.5 years of age. The DSMC will have the responsibility for deciding that the study should be stopped early if evidence accumulates that there are serious risks to patient safety.

5.6 Missing Data for the Visual Acuity Assessment

The problem of a patient having vision below the level that can be measured was discussed in Section 4.4.5. In addition, there are several scenarios that could result in missing data and other difficulties regarding the visual acuity assessment. The scenarios and the proposed methods for handling the problems are as follows:

- 1) Uncooperative Patient Without Evidence for Poor Vision Despite efforts to accomplish a visual acuity assessment, including scheduling 3 different testing sessions, it may happen that the child is uncooperative to an extent that precludes obtaining a visual acuity assessment even though the child can see. The determination that an uncooperative patient can see will be based on the observed behavior of the child relative to visual tasks, the qualitative visual assessment of the IATS physician, and the parent's description of the child's behavior relative to visual tasks
 - a) If the vision tester, in consultation with Dr. Hartmann (if Dr. Hartmann is not the vision tester), concludes that the child has measurable vision in the fellow eye, then for statistical analysis an imputed value will be used: the median logMAR value among all fellow eyes in the study whose visual acuity could be measured.
 - b) If the vision tester, in consultation with Dr. Hartmann (if Dr. Hartmann is not the vision tester), concludes that the child has measurable vision in the aphakic/pseudophakic eye, then for statistical analysis, the following imputed value will be used: the logMAR value among eyes with the same treatment assignment with a percentile score equal to the percentile score of the patient's vision in the fellow eye. The use of this value is an attempt to utilize the correlation between a patient's eyes. However, there is the assumption that the reason for the child being uncooperative for the treated eye visual acuity assessment is unrelated to the vision in that eye. If the fellow eye has poor vision, then the median logMAR value among aphakic/pseudophakic eyes with the same treatment assignment will be used.
- 2) Poor Vision in the Fellow Eye For the infant to be eligible for the study, the fellow eye must not have any abnormal conditions. However, at the time of the visual acuity assessment, the vision may be poor in the fellow eye. One possible reason is that since the baseline examination the child has experienced trauma that has affected the vision in the fellow eye. Another possible reason is that there is a medical condition affecting the vision in the fellow eye that may have been missed at the baseline examination or that developed since the baseline examination. The primary outcome is the interocular difference in visual acuity and the expectation is that the vision in the fellow eye will be "normal". If the vision in the fellow eye is not normal because of trauma or some other condition, a large interocular difference favoring the treatment group to which the patient was assigned will result. Although such occurrences are expected to be extremely rare and randomization may provide balance between the treatment groups, we will also investigate the use of the following imputed value for the vision in the fellow eye: the median logMAR value among fellow eyes for which visual acuity could be measured. The sensitivity of the analysis comparing treatments to the use of the imputed value will be assessed.
- 3) Patient Not Having Visual Acuity Assessment It may happen that the traveling vision tester never examines a particular patient. We expect that this will only happen if the patient is lost to follow-up before the visual acuity assessment. An option would be to incorporate the information from the qualitative visual acuity assessment done at the 3-monthly visits by the physician before the patient was lost. The information from these assessments will be limited since the possible values are the 3 ordered categories: No Light Perception, Light Perception,

Fix and Follow. If the patient is lost before any post-operative qualitative visual assessment is done the patient will not be included in the analysis. Otherwise, we will investigate using imputed values for the missing data as follows:

- a) If the physician has classified the vision in a patient's eye as less than Fix and Follow at the last visit before the patient was lost then we will use the imputed logMAR value 2.6464.
- b) If the physician has classified the vision in a patient's eye as Fix and Follow we will determine an imputed value according to the methods described in scenario 1) above. We will compare the results of the analysis comparing treatments using the imputed values for lost patients to the results when lost patients are not included in analysis. A disadvantage of using the information from the 3-monthly assessments is the potential for bias since the traveling vision tester will not have seen the patient.

Chapter 6

Parenting Stress

Background:

Quality of life is an important construct for families and young children. In very young children, limited measures of quality of life that have been validated in a variety of settings and populations are available. However, parenting stress is a key measure of quality of life in families with infants and young children for which well-validated measures are available.

Parenting stress, defined as stress associated with the parenting role, has been recognized for many years as an important construct in the fields of pediatrics, pediatric psychology, and child development. Low levels of parenting stress during the first 3 years of a child's life are critical to the child's emotional/behavioral development and to the developing parent-child relationship. Excessive parenting stress can lead to dysfunctional parenting, which in turn can lead to behavioral and emotional problems in children. High levels of self-reported parenting stress have been empirically linked with infants' and toddlers' insecure attachment to the mother (Moran & Pederson, 1998; Hadadian & Merbler, 1996), maternal depression (Frankel & Harmon, 1996), and parent-reported behavioral problems (Goldberg et al., 1997).

Parents of infants with congenital conditions, chronic illnesses, and disabilities report greater levels of parenting stress on the Parenting Stress Index (PSI) than control groups (Goldberg et al., 1990; Pelchat et al., 1999; Singer et al., 1999), mainly on the domain assessing perceptions of the child's behavior (Child Domain). Longitudinal studies of parenting stress indicate that stress levels remain high for parents of children with disabilities or chronic illness (Singer et al., 1999; Warfield et al., 1999).

Treatment for unilateral congenital cataract is believed to be stressful for parents because of: (1) the requirement for early surgery, (2) the requirement for early and intensive treatment (including requiring the caregiver to place and maintain a contact lens in the aphakic eye, and patching of the "good" eye), (3) the fact that, even with early treatment, a majority of children with unilateral congenital cataracts develop poor visual acuity in the aphakic eye (Robb et al., 1987; Cheng et al., 1991; Maurer & Lewis, 1993; Lewis et al., 1995), and (4) treatment that may become even more onerous as the child gets older, especially if he/she develops amblyopia. High levels of parenting stress in this population may have negative implications for treatment, as stressed parents may "give up" on patching, contact lens wear or both, settling for suboptimal vision in the aphakic eye.

Proposed changes in treatment for congenital cataracts, such as implantation of an intraocular lens (IOL) at the time of cataract removal, may alleviate some of the parenting stress associated with caring for a child with a unilateral congenital cataract. Given equivalent visual outcomes for the two treatments, the option associated with reduced parenting stress may be preferred by clinicians and parents.

The goal of this aspect of the study is to compare parenting stress after surgery (i.e., three months, and again eight-fourteen months after surgery) reported by parents of children receiving traditional therapy (aphakic contact lenses) with those randomly assigned to receive a primary IOL.

Administration Plan:

The Parenting Stress measures will consist of the long version of the Parenting Stress Index and a short, condition-specific parenting stress measure, the Ocular Treatment Index. The Parenting Stress Index (PSI; Abidin, 1986) is a well-researched, standardized, self-report measure of parenting stressors consistently related to dysfunctional parenting. The 120-item scale yields two factor-based scores, a Child Domain score and a Parent Domain score, as well as a Total Stress score. The Child Domain includes six subscales (Distractibility/Hyperactivity, Adaptability, Reinforces Parent, Demandingness, Mood, Acceptability) and the Parent Domain includes seven subscales (Competence, Isolation, Attachment, Health, Role Restriction, Depression, Spouse). The Life Stress scale assesses situational stress (e.g., death of a relative, loss of a job) outside the parent-child relationship. The five response choices for each item range from “strongly agree” to “strongly disagree.” For the scale as a whole, the two domains, and the thirteen subscales, higher scores indicate greater stress.

The PSI was normed on a sample of 2,633 mothers recruited primarily from a private group pediatric practice. Performance on the PSI is interpreted via age-based percentile scores derived from the frequency distribution of the normative sample (1 to 12 year olds). All PSI scores have well-established internal consistency and test-retest reliability. Factor analyses indicate that each subscale measures a moderately distinct source of stress. The construct and concurrent validity of PSI scores are supported by significant correlations between Parent Domain subscale scores and parental responsiveness (Onufrak, Saylor, Taylor, Eyberg, & Boyce, 1995) and by significant correlations between Child Domain scores and parent and teacher ratings of children’s behavior problems (Lafiosca & Loyd, 1987). Discriminant validity is supported by the scale’s ability to differentiate parents of children with chronic illness, handicaps, or behavior problems from those in a control group (e.g., Abidin, 1995; Kazak & Marvin, 1984).

However, disease-specific measures of psychological variables are often preferred to general measures because they focus on domains most relevant to the target disease. At the time this project was developed, there were no published reports of disease-specific measures of parenting stress or quality of life for parents of children with congenital cataract or other ophthalmic conditions. As the PSI does not measure parenting stressors specific to the care of a child with visual impairments or ocular anomalies, we developed an illness-specific parenting stress measure called the Ocular Treatment Index (OTI). The OTI consists of 28 Likert-type items with five response choices ranging from “strongly agree” to “strongly disagree”. All items were written by an interdisciplinary research team (pediatric ophthalmologist, epidemiologist, clinical child psychologist, and orthoptist) based upon clinical experience with cataract patients, a focus group with parents of children with UCC, and familiarity with the child development and pediatric psychology literatures. Preliminary validation of this measure has been published and a slightly modified version of the measure has been used in the Amblyopia Treatment Study.

After review of the proposed scales, a few items were added by the IATS Advisory Committee and the parents of two young children with bilateral congenital cataracts. In pilot studies, internal consistency between the 28 items on the scale had an observed Cronbach's alpha of 0.94. The observed range on the scale was 47 to 123 versus a theoretical range of 28-140. The mean total score was 85.2, with a standard deviation of 20. This suggests a good distribution of scores. Further, as predicted a priori, the OTI was positively correlated with 11 of 13 PSI subscales, but was not associated with either age or the Life Stress subscale of the PSI.

We will administer the Parenting Stress Index and the OTI to parents at 3 months after surgery and at the first 3-monthly visit following the visual acuity assessment. These two questionnaires will be administered as a single "caregiver questionnaire" in English or Spanish depending on the language preference of the primary caregiver. The caregiver questionnaire will be given to the primary caregiver to be completed at the office visit. Upon completion of the caregiver questionnaire, the caregiver will seal the questionnaire in an envelope for the clinic coordinator to mail to the DCC.

Analysis:

Power considerations and the statistical analysis of the parenting stress outcome are presented in Chapter 5 Statistical Considerations.

Procedure for Handling Elevated Parenting Stress Index (PSI) Scores:

DCC staff will score the PSI within one week of receipt. If a participant's Total Stress raw score is at or above 260 (> 85th percentile for 1 year olds), DCC data entry staff will alert the IATS psychologist within 24 hours. The psychologist will examine the participant's PSI profile within 48 hours to determine whether the participant should be contacted by phone to discuss a referral for mental health services. The cut-off score of 260 is recommended by the developers of the PSI (Abidin, 1995). Reports to the DSMC every six months will include the number of participants with a score > 260, the number that are called by the psychologist, and the outcome of those calls.

The decision to contact a participant due to an elevated PSI Total Stress score is complex and involves clinical judgment as well as an understanding of scale psychometric properties.

Examples include:

- The elevated PSI Total Stress score may reflect an elevated Child Domain score, with Parent Domain and Life Stress scores in the normal range. In this case, it is likely that child characteristics, rather than parent characteristics, are primarily contributing to the stress in the parent-child system. A referral for mental health services for the parent may not be needed.

- If the elevated PSI Total Stress score is accompanied by a Life Stress raw score above 17, the parent is experiencing a considerable degree of stress both within and outside the parent-child relationship, and a referral for mental health services may be warranted.
- If the elevated PSI Total Stress score includes an elevated Health or Depression subscale score, the parent may be experiencing significant clinical depression or health problems. The parent may be advised to talk with his or her health care provider, and/or a referral to mental health services may be given.

References for Parenting Stress

- Abidin, R.R. (1995). Parenting Stress Index: Professional Manual (3rd Ed.). Odessa, FL: Psychological Assessment Resources, Inc.
- Frankel, K.A., & Harmon, R.J. (1996). Depressed mothers: They don't always look as bad as they feel. Journal of the American Academy of Child & Adolescent Psychiatry, 35, 289-298.
- Goldberg, S., Janus, M., Washington, J., Simmons, R.J., MacLusky, I., & Fowler, R.S. (1997). Prediction of preschool behavioral problems in healthy and pediatric samples. Journal of Developmental & Behavioral Pediatrics, 18, 304-313.
- Goldberg, S., Morris, P. Simmons, R.J., Fowler R.S., et al. (1990). Chronic illness in infancy and parenting stress: A comparison of three groups of parents. Journal of Pediatric Psychology, 15, 347-358.
- Hadadian, A., & Merbler, J. (1996). Mother's stress: Implications for attachment relationships. Early Child Development & Care, 125, 59-66.
- Hauenstein, E.J., Marvin, R.S., Snyder, A.L., & Clarke, W.L. (1989). Stress in parents of children with diabetes-mellitus. Diabetes Care, 12, 18-23.
- Innocenti, M.S., Huh, D., & Boyce, G.C. (1992). Families of children with disabilities: Normative data and other considerations on parenting distress. Topics in Early Childhood Special Education, 12, 403-427.
- Kazak, A.E., & Marvin, R.S. (1984). Differences, difficulties and adaptation: Stress and social networks in families with a handicapped child. Family Relations, 33, 1-11.
- Lafiosca, T., & Loyd, B. (1986). Defensiveness and the assessment of parental stress and anxiety. Journal of Clinical Child Psychology, 15, 254-259.
- La Greca, A.M., & Lemanek, K.L. (1996). Editorial: Assessment as a process in pediatric psychology. Journal of Pediatric Psychology, 21, 137-151.

Moran, G., & Pederson, D.R. (1998). Proneness to distress and ambivalent relationships. Infant Behavior & Development, 21, 493-503.

Onufrak, B., Saylor, C.F., Taylor, M.J., Eyberg, S.M., & Boyce, G.C. (1995). Determinants of responsiveness in mothers of children with intraventricular hemorrhage. Journal of Pediatric Psychology, 20, 587-599.

Pelchat, D., Ricard, N., Bouchard, J-M, Perreault, M., Saucier, J-F, Berthiaume, M., & Bisson, J. (1999). Adaptation of parents in relation to their 6-month-old infant's type of disability. Child: Care, Health & Development, 25, 377-397.

Robson, A.L. (1997). Low birth weight and parenting stress during early childhood. Journal of Pediatric Psychology, 22, 297-311.

Singer, L.T., Salvator, A., Guo, S., Collin, M., Lilien, L., & Baley, J. (1999). Maternal psychological distress and parenting stress after the birth of a very low-birth-weight infant. JAMA, 281, 799-805.

Smith, K.H., Baker, D.B., Keech, R.V. et al (1991). Monocular congenital cataracts: Psychological effects of treatment. Journal of Pediatric Ophthalmology and Strabismus, 28, 245-249.

Smith, L.K., Thompson, J.R., Woodruff, G., & Hiscox, F. (1995). Factors affecting treatment compliance in amblyopia. Journal of Pediatric Ophthalmology and Strabismus, 32, 98-101.

Warfield, M.E., Krauss, M.W., Hauser-Cram, P., Upshur, C.C., & Shonkoff, J.P. (1999). Adaptation during early childhood among mothers of children with disabilities. Journal of Developmental and Behavioral Pediatrics, 20, 9-16.

Table 1
Items on the Revised Ocular Treatment Index (OTI)

1. My child's poor vision gets in the way of his/her learning.
2. I am afraid that my child will never have good vision.
3. I don't like the way my child's treated eye looks.
4. Taking my child to the eye doctor is stressful.
5. I have trouble putting on my child's patch.
6. The patch irritates my child's skin.
7. I worry that my child will become injured when the patch is on.
8. I worry that my child will take his/her patch off when I am not around.
9. Patching is a source of tension or conflict in my marriage.
10. My child is much less active when patched than when not patched.
11. I worry that my child will be teased when he/she is wearing an eye patch.
12. My child can see well with his/her patch on.^a
13. I have trouble keeping the patch on my child.
14. My child is clumsy and uncoordinated when patched.
15. I worry about what others may think when they see my child with his/her patch on.
16. I have trouble getting my child to wear the patch.
17. Patching is a source of tension or conflict in my relationship with my child.
18. I worry that my child does not wear the patch enough.
19. I worry that my child's contact lenses or glasses will become broken.
20. I worry that my child will be injured because of wearing his/her contact lenses or glasses.
21. Wearing glasses or contact lenses is comfortable for my child.^a

- 22. Replacing my child's glasses or contact lenses is expensive.
 - 23. I worry that my child's contacts will fall out or glasses will fall off during the day.
 - 24. My child's eye becomes pink or bloodshot from wearing his/her contact lenses or glasses.
 - 25. I can't leave my child with other people because I am afraid that he/she will lose his/her contacts or glasses.
 - 26. I am worried that my child's glasses or contact lenses will become scratched.
-

Note. ^a Item is reversed in scoring.

Table 2
Correlations of Parenting Stress Index (PSI) Scores
with the Ocular Treatment Index (OTI)

PSI Child Domain summary score	.46 ^b
Distractibility subscale	.23
Adaptibility subscale	.38 ^c
Reinforces Parent subscale	.44 ^b
Demandingness subscale	.54 ^a
Mood subscale	.42 ^b
Acceptibility subscale	.38 ^c
PSI Parent Domain summary score	.59 ^a
Competence subscale	.53 ^a
Isolation subscale	.41 ^b
Attachment subscale	.07
Health subscale	.36 ^c
Role Restriction subscale	.74 ^a
Depression subscale	.38 ^c
Spouse subscale	.55 ^a
PSI Total Score	.55 ^a

Note. ^a $p < .01$, ^b $p < .05$, ^c $p < .10$.

Chapter 7

Adherence

7.1 General Principles

Parental adherence to the treatment regimen of patching and visual correction with contact lenses or spectacles is believed to play an important role in the visual outcome of children with unilateral congenital cataracts (UCC) (Birch & Stager, 1988). In fact, it is possible that any improved visual acuity among children with a UCC who receive a primary IOL may be enhanced by improved adherence to the treatment regimen. Assessing use of the patch, contact lens and spectacles will be important to determine if:

- Improved visual outcome is associated with better adherence to the treatment regimen among children receiving a single type of treatment (i.e., among aphakic children or among pseudophakic children),
- Adherence is better in pseudophakic than aphakic children, or vice versa, and
- Adherence to the treatment protocol contributes to a better visual outcome among pseudophakic children than aphakic children, or vice versa.

We will use parental reports to assess adherence to the patching regimen and use of contact lenses and/or spectacles. Neither automated adherence tools nor standardized questionnaires to assess adherence to patching and visual correction among preschool-aged children are available. Further, limited data exist on the most valid type of parental questionnaire to assess adherence to a medical regimen among preschool-aged children. Most assessments of adherence to medical regimens use pill counts, which cannot be applied to assessment of patching or visual correction. “Smart Patches” to assess adherence with patching regimens are under development. However, at this point they are neither acceptable to parents nor able to assess adherence with both patching and visual correction.

Therefore, we modeled our assessment of adherence after dietary assessments, which have been used in a variety of epidemiologic studies, including those of dietary assessment of preschool-aged children. Many studies of diet have used a combination of a series of 24-hour dietary recalls and 3- to 7-day weighed dietary records.

Two types of parental report of adherence to recommended patching and visual correction will be obtained in this study: 1) an eye-care diary and 2) a quarterly 48-hour recall interview.

7.2 Results of Pilot Study of Adherence Measures

In our randomized pilot study we obtained both interview and diary data on 11 of 17 subjects. Interview and diary information provided similar data on patching compliance (i.e., within 5%) for 3 of the 11 subjects for whom both data sources were available. Another two subjects

provided similar information if the fact that, based on the diary, they were patching all day, every other day was taken into account. The two sources estimated a different amount of patching for the remaining six. For two subjects, the amount of patching was higher when reported on the interview, and for four subjects, the amount of reported patching was higher on the diary. These differences may reflect the fact that these data were collected over different time periods and/or different degrees of accuracy. We believe that this information justifies our proposal to assess compliance using both interviews and diaries.

First, it was possible to interview most of the caregivers, usually with little difficulty. Secondly, we were able to contact women and provide them with a connection to the study and study staff. In one case, this resulted in the child getting needed visual correction. Finally, it appears that some women have an easier time reporting information on an interview when they are being cued than on a diary. For example, one woman obviously failed to document daytime naps on her diary that she did report on the interview. On the other hand, some women were unable to report on treatment during certain hours of the day because another caregiver was caring for the child. These women were able to get this information from the caregiver on the diary. Further, we were able to use these methods to assess not only compliance with patching, but also patching with visual correction. Such assessment would not be possible with some other automated types of compliance assessment.

7.3 Eye-Care Diary

Two types of eye-care diaries will be kept:

48-Hour Eye-Care Diary - At the one month visit, the parent and/or primary caregiver will complete an eye-care diary to report patching and visual correction over the previous 48-hours. At this visit, the clinic coordinator will provide training in how to complete this diary. The coordinator and the caregiver will review an example scenario and together they will complete a diary based on this scenario. The caregiver will then be provided the opportunity to ask questions on completing the diary. The caregiver will then complete a diary reporting patching, sleeping and visual correction for the previous 48-hours. The diary at the one-month visit will be used, in part, to train the Parents/Caregivers on how to complete the diary. After the caregiver completes the 48-hour diary, the diary will be placed in a sealed envelope and mailed to the DCC by the Clinical Coordinator.

7-Day Eye-Care Diary – A 7-Day Eye Care Diary will be mailed 1-month after both the 1-month visit and the visual acuity assessment visit. This diary will be completed, prospectively by all caregivers over the 7-days starting the following Sunday. 7-Day Eye Care Diaries will then be completed annually when the child is 25, 37 and 49 months of age. The 7-Day Eye Care Diaries will prospectively document wake times, patching and visual correction use over a one-week period starting Sunday morning. The diaries will be mailed from the DCC to the primary caregiver, along with instructions. After completion, the caregiver will mail the 7-Day Eye Care Diary directly back to the DCC.

7.3.1 Administration of Eye-Care Diary

48-Hour Eye-Care Diary

At the 1-month visit, the Clinic Coordinator will go over an example day with the parent, and together they will complete an example eye-care diary before the caregiver completes the 48-hour eye-care diary. This will provide the parent or caregiver with training on how to complete the eye-care diary. The parent should be allowed to ask questions while he/she is working with the coordinator to complete the example diary. The parent/caregiver will also be able to take this "example" diary and scenario home to refer to when completing the 7-day eye-care diary. The Clinic Coordinator should record comments about the training session and completion of the eye-care diary in the comments section, and mail the 48-hour Eye-Care diary to the DCC as soon as possible after the visit.

At the 1-month visit the Clinic Coordinator should remind the caregiver that:

- The DCC will be sending 7-day eye-care diary to the parent approximately in approximately 1 month. The diary should be prospectively completed throughout the week starting Sunday morning, rather than completed at the end of the week.
- A quarterly 48-hour recall interview of patching, visual correction and sleeping will be completed over the telephone.

7-Day Eye-Care Diary

The 7-Day eye-care diary is intended to be completed prospectively every year. This should minimize errors related to changing care-givers and retrospectively recalled data.

The eye-care diary will be mailed from the DCC. Each Thursday the DCC will generate a list of all subjects whose 1-month visit or Visual Acuity Assessment Visit was 4 weeks prior. The DCC will also generate lists of participants who are turning 25, 37, or 49 months of age. The DCC will then mail the 7-Day Eye Care Diary the following Monday. On the selected day of the month, the diaries will be mailed to the respondent's home address. The mailing will include: The eye-care diary, a self-addressed stamped, envelope and a cover letter.

The caregiver will have received instruction on how to complete the eye-care diary at the 1 month follow-up visit. The cover letter sent with the diary will re-introduce the eye-care diary, and explain that the parent is to start recording patching and visual correction information for 7 complete days, starting Sunday morning. The DCC will contact the caregiver on Saturday to make sure they had received the diary and to remind them to start keeping the diary the next morning. Over, the subsequent week, the primary caregiver and all other caregivers are to record all wake, sleep, patch on, patch off, contact lens on, contact lens off, spectacles, and spectacles off times starting when the child wakes the next morning.

When the diary is completed, the parent is to return the diary, by mail, in a self-addressed, stamped envelope provided with the diary. Upon receipt, the DCC Staff will record that the diary has been returned and review the form for completeness. The DCC will contact the parent about any missing or illegible information and then fax the completed form into the DCC computer for entry into the database.

Two weeks after the date that the diaries were mailed, the DCC staff will identify all diaries that have not yet been returned. The DCC will contact parents by telephone to remind them to complete the diary and return it, whenever a diary is not returned within 14 days.

7.4 48-Hour Adherence Interview

Staff at the DCC will conduct a telephone interview of patching adherence and use of visual correction approximately every 3 months, starting 3 months after surgery. The adherence interview is a 30-minute, structured telephone interview designed to gain information about the proportion of time while awake that the child wore the patch and visual correction during the previous 48-hours. Because patching can be prescribed for 50% of waking hours every day or all day every other day, it is important that this interview be a true "48-hour" recall rather than the previous day. The structure of the interview uses questions about the child's activities, sleep and wake times, meal times, bath times, etc. as anchors to improve recall. For example, research has shown that memory can be improved by asking the caregiver to recall what time the child woke, when he/she was dressed, and when he/she had breakfast, and then asking if the child was wearing his/her patch, contact lens, glasses, at these times.

At the end of each month, the DCC will generate two lists of subjects: 1) all subjects whose enrollment date was 3, 9, 15, 21, 27, 33, 39, or 45 months previous, and 2) all subjects whose enrollment date was 6, 12, 18, 24, 30, 36, 42, or 48 months previous.

For each of these two lists, the DCC will then randomly generate a number from 1 to 31 (28 for February, 30 for April, June, September and November) indicating which day of the month (i.e., the 1st, 2nd, 3rd, or 4th) the interviews will be conducted. The DCC will start conducting the adherence interviews for each group of participants on these selected days. If the date selected for the interview overlaps the dates that the 7-Day Eye Care Diary is being kept the target date for the interview will be adjusted by one week (i.e., Date + 7).

If the DCC is unable to complete an interview on the day for that participant, they will attempt to conduct the interview the next day for four consecutive days. However, in order to obtain as much information about both weekend and week days as possible, if the selected day is a weekend day (i.e., Saturday or Sunday), the interviews will be attempted on four consecutive weekend days. If the selected day is a weekday, the interviews will be attempted on four consecutive weekdays. If the interview is not completed after the four attempts the DCC will make two additional attempts to conduct the interview over the next week, regardless of the day of the week. If the interview has still not been completed after this time, the participant will be considered a potential lost to follow-up, and the DCC will contact the clinical center in an

attempt to locate the participant. All contact with a patient's family will be recorded on a Contact Log Form.

Chapter 8

Certification of Personnel

8.1 Certification of Surgeons

The certification process for an IATS surgeon will include:

1. Completion of a pediatric ophthalmology fellowship.
2. Experience performing cataract surgery including the placement of IOLs in children.
3. Availability of an anesthesiologist experienced in managing infants.
4. Approval by the NEI of the surgeon's clinical center as an IATS center.
5. Passing a certification examination that will be prepared by the study chair. The examination will be placed on a secure website by the Jaeb Center and administered online. The Jaeb Center will maintain the website and grade the examinations. The certification examination will ensure that the surgeon is familiar with IATS protocol.
6. Submission of a videotape to Ed Wilson, MD, of the surgeon performing cataract surgery with IOL implantation on a child less than two years of age. The surgeon should follow the IATS surgical protocol during the procedure.

After the completion of the steps above, the surgeon will be given a 3-digit certification number by the DCC. The surgeon will then be eligible to enroll patients in IATS.

Recertification of Surgeons

Surgeons will be required to provide a video of every IATS enrollment surgery as a means of monitoring adherence to the surgical protocol. At least one video per year must be of an IATS protocol IOL implantation. If an IOL has not been implanted in an enrolled patient in the previous year, the surgeon must provide a video of a protocol IOL implantation in a young child in order to maintain certification.

8.2 Certification of Clinical Coordinators

The certification process for an IATS clinical coordinator will include:

1. Reading the IATS Manual of Procedures and Protocol.
2. Passing the IATS certification examination online. The certification examination will be the same one taken by the IATS surgeons and will be maintained on a secure website by the Jaeb Center.

8.3 Certification of Traveling Examiners

The traveling examiners who will evaluate ocular motility and visual acuity (at Age 12 months) will be trained and certified by E. Eugenie Hartmann, PhD.

The certification process for the traveling examiners will include:

1. A 3-month training period including:
 - A. Study of the Teller Acuity Card manual
 - B. Supervised practice in testing normal infants and children

- C. Supervised practice in testing pediatric patients with a history of cataracts, strabismus, and/or nystagmus
2. Passing a certification examination that will include:
 - A. Evaluation of inter-observer test/retest reliability for Teller Acuity Cards between the traveling examiner and experienced laboratory personnel
 - B. Passing a certification examination prepared by E. Hartmann, PhD, to ensure familiarity with all details of the acuity testing procedures and the IATS acuity protocol
 3. On-going reliability checks will be obtained between E. Eugenie Hartmann, PhD and the traveling examiner at the Visual Testing Center. These assessments will be conducted at regular intervals, either in terms of time or number of acuity assessments completed by the traveling examiner, whichever is deemed more appropriate during the course of the study to maintain quality control of the acuity testing. Specifically, the traveling examiner and Dr. Hartmann will conduct at least one reliability session every two months or for every 6 infants tested for the study.

8.4 Certification of Contact Lens Professionals

The certification process for a contact lens *professional* to fit infants enrolled in IATS will include:

1. Reading the IATS Manual of Procedures and Protocol
2. Passing the IATS contact lens certification examination online. The certification examination will be prepared by the study headquarters and placed online by the Jaeb Center at a secure website. The Center will communicate by e-mail whenever a contact lens *professional* has passed the examination and is therefore certified.

**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.

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 et 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

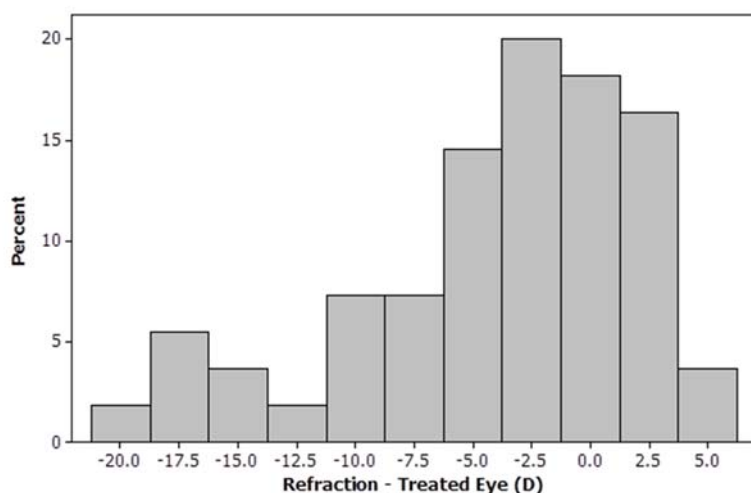
During childhood, the human eye elongates and the cornea and the crystalline lens flatten. When the biometrics of the growing eye are perfectly calibrated, the eye remains emmetropic. However, if the crystalline lens is removed surgically, the corneal flattening that occurs in early childhood cannot 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 \pm 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 refractive 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 media 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 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 ReadAlyzer™ 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, Medtronic 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 Tonpen are normal, no further testing will be performed. However, if the IOP is elevated (>21 mmHg) with ICare and/or Tonpen 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 et 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.

Data Capture, Flow and Handling

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

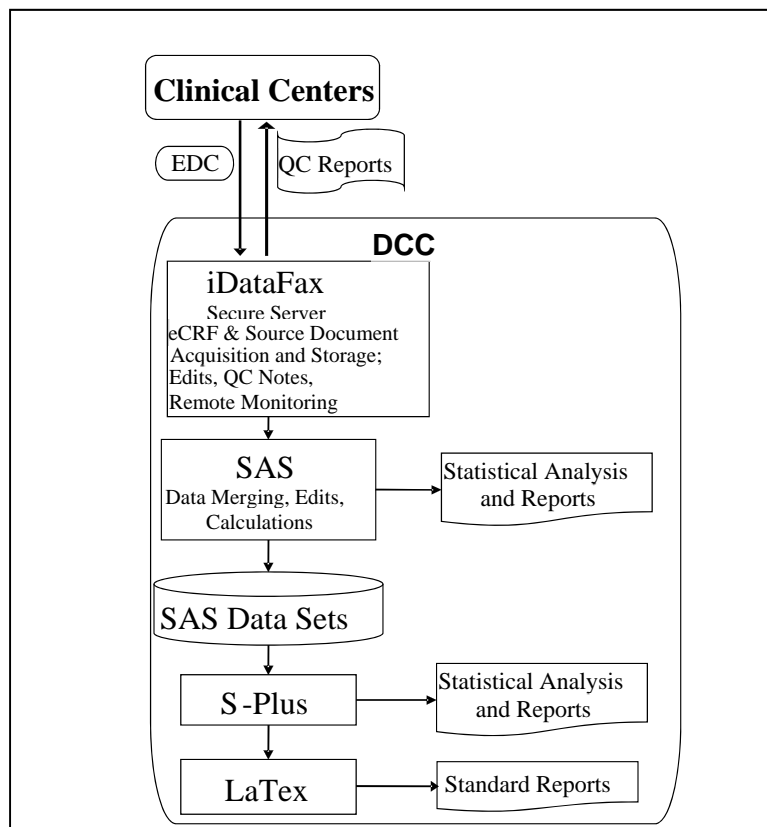
pending central review. The DCC clinical data manager will review the eCRF edits on a weekly basis and the queries will be either reinstated for further clarification or marked as resolved. iDataFax maintains an audit trail of eCRF edits made by both clinical center and DCC personnel.

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.

BIBLIOGRAPHY AND REFERENCES CITED/PROGRESS REPORT PUBLICATION LIST

a. Bibliography and References Cited

- Abidin, R. R. (1983). Parenting Stress Index: Manual, Administration Booklet and Research Update. Charlottesville, VA, Pediatric Psychology Press.
- Akaike, H. (1974). "A new look at the statistical model identification." *Automatic Control, IEEE Transactions*, 19(6): 716-723.
- Asrani, S., S. Freedman, V. Hasselblad, et al. (2000). "Does primary intraocular lens implantation prevent "aphakic" glaucoma in children?" *J AAPOS* 4(1): 33-39.
- Autrata, R., J. Rehurek and K. Vodickova (2005). "Visual results after primary intraocular lens implantation or contact lens correction for aphakia in the first year of age." *Ophthalmologica* 219(2): 72-79.
- Bailey, I. L., A. J. Jackson, H. Minto, et al. (2012). "The Berkeley Rudimentary Vision Test." *Optom Vis Sci*.
- Beck, A. D., S. F. Freedman, M. J. Lynn, et al. (2012). "Glaucoma-related adverse events in the Infant Aphakia Treatment Study: 1-year results." *Arch Ophthalmol* 130(3): 300-305.
- Beck, R. W., P. S. Moke, A. H. Turpin, et al. (2003). "A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol." *Am J Ophthalmol* 135(2): 194-205.
- Beller, R., C. S. Hoyt, E. Marg, et al. (1981). "Good visual function after neonatal surgery for congenital monocular cataracts." *Am J Ophthalmol* 91(5): 559-565.

- BenEzra, D. (1996). "Cataract surgery and intraocular lens implantation in children, and intraocular lens implantation in children." *Am J Ophthalmol* **121**(2): 224-226.
- Biglan, A. W. (2011). "Why is there an Infant Aphakia Treatment Study (IATS)?" *J AAPOS* **15**(5): 413-414.
- Birch, E. E., C. Cheng, D. R. Stager, Jr., et al. (2005). "Visual acuity development after the implantation of unilateral intraocular lenses in infants and young children." *J AAPOS* **9**(6): 527-532.
- Birch, E. E., C. Cheng, C. Vu, et al. (2010). "Oral reading after treatment of dense congenital unilateral cataract." *J AAPOS* **14**(3): 227-231.
- Birch, E. E., S. F. Strauber, R. W. Beck, et al. (2009). "Comparison of the amblyopia treatment study HOTV and the electronic-early treatment of diabetic retinopathy study visual acuity protocols in amblyopic children aged 5 to 11 years." *J AAPOS* **13**(1): 75-78.
- Bode, S. F., T. Jehle and M. Bach (2011). "Pattern electroretinogram in glaucoma suspects: new findings from a longitudinal study." *Invest Ophthalmol Vis Sci* **52**(7): 4300-4306.
- Chak, M. and J. S. Rahi (2008). "Incidence of and factors associated with glaucoma after surgery for congenital cataract: findings from the British Congenital Cataract Study." *Ophthalmology* **115**(6): 1013-1018 e1012.
- Chen, T. C., D. S. Walton and L. S. Bhatia (2004). "Aphakic glaucoma after congenital cataract surgery." *Arch Ophthalmol* **122**(12): 1819-1825.
- Cotter, S. A., R. H. Chu, D. L. Chandler, et al. (2003). "Reliability of the electronic early treatment diabetic retinopathy study testing protocol in children 7 to <13 years old." *Am J Ophthalmol* **136**(4): 655-661.
- Dahan, E. and M. U. Drusedau (1997). "Choice of lens and dioptric power in pediatric pseudophakia." *J Cataract Refract Surg* **23 Suppl 1**: 618-623.
- DeVaro, J. M., E. G. Buckley, S. Awner, et al. (1997). "Secondary posterior chamber intraocular lens implantation in pediatric patients." *Am J Ophthalmol* **123**(1): 24-30.
- Dobson, V., G. E. Quinn, R. M. Siatkowski, et al. (1999). "Agreement between grating acuity at age 1 year and Snellen acuity at age 5.5 years in the preterm child. Cryotherapy for Retinopathy of Prematurity Cooperative Group." *Invest Ophthalmol Vis Sci* **40**(2): 496-503.
- Dobson, V., G. E. Quinn, B. Tung, et al. (1995). "Comparison of recognition and grating acuities in very-low-birth-weight children with and without retinal residua of retinopathy of prematurity. Cryotherapy for Retinopathy of Prematurity Cooperative Group." *Invest Ophthalmol Vis Sci* **36**(3): 692-702.
- Draws, C., M. Celano, D. A. Plager, et al. (2003). "Parenting stress among caregivers of children with congenital cataracts." *J AAPOS* **7**(4): 244-250.
- Egbert, J. E., S. P. Christiansen, M. M. Wright, et al. (2006). "The natural history of glaucoma and ocular hypertension after pediatric cataract surgery." *J AAPOS* **10**(1): 54-57.
- El-Dairi, M. A., S. Holgado, S. G. Asrani, et al. (2009). "Correlation between optical coherence tomography and glaucomatous optic nerve head damage in children." *Br J Ophthalmol* **93**(10): 1325-1330.
- Gilbert, C. and A. Foster (2001). "Childhood blindness in the context of VISION 2020--the right to sight." *Bull World Health Organ* **79**(3): 227-232.
- Haargaard, B., C. Ritz, A. Oudin, et al. (2008). "Risk of glaucoma after pediatric cataract surgery." *Invest Ophthalmol Vis Sci* **49**(5): 1791-1796.
- Hiatt, R. L. (1998). "Rehabilitation of children with cataracts." *Trans Am Ophthalmol Soc* **96**: 475-515; discussion 515-477.
- Holmes, J. M., R. W. Beck, M. X. Repka, et al. (2001). "The amblyopia treatment study visual acuity testing protocol." *Arch Ophthalmol* **119**(9): 1345-1353.
- Khan, A. O. and S. Al-Dahmesh (2009). "Age at the time of cataract surgery and relative risk for aphakic glaucoma in nontraumatic infantile cataract." *J AAPOS* **13**(2): 166-169.

- Knight, O. J., C. A. Girkin, D. L. Budenz, et al. (2012). "Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by Cirrus HD-OCT." *Arch Ophthalmol* **130**(3): 312-318.
- Kooner, K. S., J. C. Cooksey, J. B. Barron, et al. (1992). "Tonometry comparison: Goldmann versus Tono-Pen." *Ann Ophthalmol* **24**(1): 29-36.
- Kuhli-Hattenbach, C., M. Luchtenberg, T. Kohnen, et al. (2008). "Risk factors for complications after congenital cataract surgery without intraocular lens implantation in the first 18 months of life." *Am J Ophthalmol* **146**(1): 1-7.
- Lambert, S. R., E. Buckley, C. Drews-Botsch, et al. (2010). "A randomized clinical trial comparing contact lens with intraocular lens correction of monocular aphakia during infancy: Grating acuity and adverse events at age 1 year." *Arch Ophthalmol*(In press).
- Lambert, S. R., E. G. Buckley, C. Drews-Botsch, et al. (2010). "A randomized clinical trial comparing contact lens with intraocular lens correction of monocular aphakia during infancy: grating acuity and adverse events at age 1 year." *Arch Ophthalmol* **128**(7): 810-818.
- Lambert, S. R., E. G. Buckley, D. A. Plager, et al. (1999). "Unilateral intraocular lens implantation during the first six months of life." *J AAPOS* **3**(6): 344-349.
- Lambert, S. R., D. A. Plager, M. J. Lynn, et al. (2008). "Visual outcome following the reduction or cessation of patching therapy after early unilateral cataract surgery." *Arch Ophthalmol* **126**(8): 1071-1074.
- Lim, Z., K. W. Muir, L. Duncan, et al. (2011). "Acquired central corneal thickness increase following removal of childhood cataracts." *Am J Ophthalmol* **151**(3): 434-441 e431.
- Little, R. J., D'Agostino, R., Cohen, M. L., Dickersin, K., Emerson, S. S., Farrar, J. T., ... and Stern, H. (2012). "The prevention and treatment of missing data in clinical trials." *New England Journal of Medicine*, **367**(14): 1355-1360.
- Little, R. J., Long, Q., and Lin, X. (2009). "A comparison of methods for estimating the causal effect of a treatment in randomized clinical trials subject to noncompliance." *Biometrics*, **65**(2): 640-649.
- Little, R. J. and Rubin, D. B. (2002). "Statistical analysis with missing data." Hoboken, NJ: J Wiley & Sons.
- Lorenz, B. and J. Worle (1991). "Visual results in congenital cataract with the use of contact lenses." *Graefes Arch Clin Exp Ophthalmol* **229**(2): 123-132.
- Lundvall, A. and C. Zetterstrom (2006). "Primary intraocular lens implantation in infants: complications and visual results." *J Cataract Refract Surg* **32**(10): 1672-1677.
- Lupinacci, A. P., M. L. da Silva Jordao, G. Massa, et al. (2009). "Central corneal thickness in children with congenital cataract and children with surgical aphakia: a case-control study." *Br J Ophthalmol* **93**(3): 337-341.
- McClatchey, S. K. and M. M. Parks (1997). "Myopic shift after cataract removal in childhood." *J Pediatr Ophthalmol Strabismus* **34**(2): 88-95.
- Mills, M. D. and R. M. Robb (1994). "Glaucoma following childhood cataract surgery." *J Pediatr Ophthalmol Strabismus* **31**(6): 355-360; discussion 361.
- Moke, P. S., A. H. Turpin, R. W. Beck, et al. (2001). "Computerized method of visual acuity testing: adaptation of the amblyopia treatment study visual acuity testing protocol." *Am J Ophthalmol* **132**(6): 903-909.
- Muir, K. W., L. Duncan, L. B. Enyedi, et al. (2007). "Central corneal thickness: congenital cataracts and aphakia." *Am J Ophthalmol* **144**(4): 502-506.
- Mwanza, J. C., J. D. Oakley, D. L. Budenz, et al. (2011). "Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes." *Ophthalmology* **118**(2): 241-248 e241.
- Paysse, E. A., L. Camejo, M. A. Hussein, et al. (2004). "Parent-administered visual acuity testing: is it reliable and can it improve office efficiency?" *J AAPOS* **8**(4): 332-337.

- Phelps, C. D. and N. I. Arafat (1977). "Open-angle glaucoma following surgery for congenital cataracts." *Arch Ophthalmol* **95**(11): 1985-1987.
- Plager, D. A., M. J. Lynn, E. G. Buckley, et al. (2011). "Complications, adverse events, and additional intraocular surgery 1 year after cataract surgery in the infant Aphakia Treatment Study." *Ophthalmology* **118**(12): 2330-2334.
- Plager, D. A., S. Yang, D. Neely, et al. (2002). "Complications in the first year following cataract surgery with and without IOL in infants and older children." *J AAPOS* **6**(1): 9-14.
- Ram, J., N. Gupta, J. S. Sukhija, et al. (2011). "Outcome of cataract surgery with primary intraocular lens implantation in children." *Br J Ophthalmol* **95**(8): 1086-1090.
- Rice, M. L., D. A. Leske and J. M. Holmes (2004). "Comparison of the amblyopia treatment study HOTV and electronic-early treatment of diabetic retinopathy study visual acuity protocols in children aged 5 to 12 years." *Am J Ophthalmol* **137**(2): 278-282.
- Rosenbaum, P. R., and Rubin, D. B. (1983). "The central role of the propensity score in observational studies for causal effects. *Biometrika*, **70**(1): 41-55.
- Simsek, T., A. H. Mutluay, U. Elgin, et al. (2006). "Glaucoma and increased central corneal thickness in aphakic and pseudophakic patients after congenital cataract surgery." *Br J Ophthalmol* **90**(9): 1103-1106.
- Swamy, B. N., F. Billson, F. Martin, et al. (2007). "Secondary glaucoma after paediatric cataract surgery." *Br J Ophthalmol* **91**(12): 1627-1630.
- Trivedi, R. H., M. E. Wilson, Jr. and J. Facciani (2005). "Secondary intraocular lens implantation for pediatric aphakia." *J AAPOS* **9**(4): 346-352.
- Trivedi, R. H., M. E. Wilson, Jr. and R. L. Golub (2006). "Incidence and risk factors for glaucoma after pediatric cataract surgery with and without intraocular lens implantation." *J AAPOS* **10**(2): 117-123.
- Ventura, L. M., I. Golubev, W. J. Feuer, et al. (2011). "Pattern Electroretinogram Progression in Glaucoma Suspects." *J Glaucoma*.
- Webber, A. L., J. M. Wood, G. A. Gole, et al. (2008). "The effect of amblyopia on fine motor skills in children." *Invest Ophthalmol Vis Sci* **49**(2): 594-603.
- Wilson, M. E. (1996). "Intraocular lens implantation: has it become the standard of care for children?" *Ophthalmology* **103**(11): 1719-1720.

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 Ophthalmol* 2010;128:21-27. PMID3230731.
2. Lambert SR, Buckley EG, Drews-Botsch C, DuBois L, Hartmann E, Lynn MJ, Plager DA, Wilson ME and the Infant Aphakia Treatment Study Group. A randomized clinical trial comparing contact lens and intraocular lens correction of monocular aphakia during infancy: Grating acuity and adverse events at age 1 year. *Arch Ophthalmol* 2010;128:810-818. PMC--In process.
3. Wilson ME, Trivedi RH, Morrison DG, Lambert SR, Buckley EG, Plager DA, Lynn MJ and the Infant Aphakia Treatment Study Group. Infant Aphakia Treatment Study: Evaluation of cataract morphology in eyes with monocular cataracts. *J AAPOS* 2011;15:421-426. PMID3345197.

4. Morrison DG, Wilson ME, Trivedi RH, Lambert SR, Lynn MJ and the Infant Aphakia Treatment Study Group. Infant Aphakia Treatment Study: Effects of Persistent Fetal Vasculature on Outcome at 1 year of age. *JAAPOS* 2011;15:427-431. PMID3223380.
5. Plager DA, Buckley EG, Lynn MJ, Wilson ME, Lambert SR, and the Infant Aphakia Treatment Study Group. Complications, adverse events and additional intraocular surgeries in the first year following cataract surgery in the Infant Aphakia Treatment Study. *Ophthalmology* 2011;118:2330-4. PMID3230731.
6. Beck AD, Freedman S, Lynn MJ, Bothun E, Neely D, Lambert SR and the Infant Aphakia Treatment Study Group. Glaucoma-related adverse events in the infant aphakia treatment study (IATS): One year results. *Arch Ophthalmol* 2012;130:300-305. PMC--In process.
7. VanderVeen DK, Nizam A, Lynn M, Bothun ED, McClatchey SK, Weakley DR, Lambert SR and the Infant Aphakia Treatment Study Group. Predictability of IOL calculation and early refractive status in the Infant Aphakia Treatment Study. *Arch Ophthalmol* 2012;130:293-299. PMID3329400.
8. Drews-Botsch CD, Hartmann E, Celano M for the Infant Aphakia Treatment Study. Predictors of Adherence to Occlusion Therapy Three Months after Cataract Extraction in the Infant Aphakia Treatment Study. *J AAPOS* 2012;16:150-155. PMID3336096.
9. Drews-Botsch CD, Hartmann E, Kruger S, Celano M for the Infant Aphakia Treatment Study. Adherence to occlusion therapy in the six months of follow up and visual acuity among participants in the Infant Aphakia Treatment Study (IATS). *Inv Ophthal Vis Sci* 2012;53:3368-75. PMID3374623.
10. Russell B, Ward MA, Lynn M, DuBois L, Lambert SR and the Infant Aphakia Treatment Study Group. The Infant Aphakia Treatment Study Contact Lens Experience: One-Year Outcomes. *Eye & Contact lens: Science and Clinical Practice* 2012;38:234-9. PMC--In process.
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).
12. Lambert SR, Lynn MJ, Dubois LE, Cotsonis GA, Hartmann EE, Wilson ME for the Infant Aphakia Treatment Study Group. Axial elongation following cataract surgery during the first year of life in the Infant Aphakia Treatment Study. *Inv Ophthal Vis Sci* 2012;52:7539-7545. PMID: PMC3493185.
13. Bothun E, Cleveland J, Lynn MJ, Christiansen SP, Vanderveen DK, Neely DE, Kruger DJ, Lambert SR for the Infant Aphakia Treatment Study Group. One-year strabismus outcomes in the Infant Aphakia Treatment Study. *Ophthalmology* 2013;120:1227-31. PMID: In process.
14. Celano M, Hartmann EE, Drews-Botsch CD for the Infant Aphakia Treatment Study Group. Parenting stress in the Infant Aphakia Treatment Study. *Journal of Pediatric Psychology* 2013; 38(5): 484–493. PMID: PMC3666118.
15. VanderVeen DK, Trivedi RH, Nizam A, Lynn MJ, Lambert SR, for the Infant Aphakia Treatment Study Group. Predictability of Intraocular Lens Power Calculation Formulae in Infantile Eyes with Unilateral Congenital Cataract: Results

- from the Infant Aphakia Treatment Study. *Am J Ophthalmol* 2013; 156:1252-1260. PMID: PMC4140419.
16. VanderVeen DK, Trivedi RH, Nizam A, Lynn MJ, Lambert SR, for the Infant Aphakia Treatment Study Group. Response to Letter to the Editor Re: Predictability of Intraocular Lens Power Calculation Formulae in Infantile Eyes with Unilateral Congenital Cataract: Results from the Infant Aphakia Treatment Study. *Am J Ophthalmol* 2014;157:1333
 17. Trivedi RH, Lambert SR, Lynn MJ, Wilson ME. The role of preoperative biometry in selecting initial contact lens power in the Infant Aphakia Treatment Study. *J AAPOS* 2014;18:251-254. PMID: PMC4080905.
 18. Infant Aphakia Treatment Study Group. A randomized clinical trial comparing contact lens to intraocular lens correction of monocular aphakia during infancy: HOTV optotype acuity at age 4.5 years and clinical findings at age 5 years. *JAMA Ophthalmology* 2014;132:676-682 PMID: PMC4138810.
 19. Felius J, Busettini C, Lynn MJ, Hartmann EE, Lambert SR for the Infant Aphakia Treatment Study Group. Nystagmus and related fixational instabilities following extraction of unilateral infantile cataract in the Infant Aphakia Treatment Study (IATS). *IOVS* 2014;55:5332-5337. PMID: In process.
 20. Bothun E, Lynn MJ, Lambert SR. Response to Letter to the Editor Re: One-year strabismus outcomes in the Infant Aphakia Treatment Study. *Ophthalmology* 2014;121:e53.
 21. Wall PB, Lee JA, Lynn MJ, Lambert SR, Traboulsi EI and the IATS Group. The effects of surgical factors on postoperative astigmatism in patients enrolled in the Infant Aphakia Treatment Study (IATS). *JAAPOS* 2014;18:417-422
 22. Plager DA, Lynn MJ, Buckley EG, Wilson ME, Lambert SR. Complications in the first 5 years following cataract surgery in infants with and without IOL in the IATS. *Am J Ophthalmol* 2014;158:892-898.
 23. Lambert SR, Lynn MJ, Hartmann EE. Response to Letter to the Editor Re: A randomized clinical trial comparing contact lens to intraocular lens correction of monocular aphakia during infancy: HOTV optotype acuity at age 4.5 years and clinical findings at age 5 years. *JAMA Ophthalmology* 2014;132:1492-1493.
 24. Kruger S, DuBois L, Becker ER, Morrison D, Wilson L, Wilson ME, Lambert SR for the Infant Aphakia Treatment Study. Cost of intraocular lens vs. contact lens treatment after unilateral congenital cataract surgery in the Infant Aphakia Treatment Study: Retrospective analysis at age 5 years. *Ophthalmology* 2015;122:288-292.
 25. Plager DA, Lynn MJ, Buckley EG, Wilson ME, Lambert SR. Response to Letter to the Editor. Re: Complications in the first 5 years following cataract surgery in infants with and without IOL in the IATS. *Am J Ophthalmol* 2014;158:1361.
 26. Hartmann EE, Stout AU, Lynn MJ, Yen KG, Kruger SJ, Lambert SR and the Infant Aphakia Treatment Study Group. Stereopsis results at 4.5 years of age in the Infant Aphakia Treatment Study. *Am J Ophthalmol*. 2015;159:64-70.

27. Hartmann EE, Lynn MJ, Lambert S. Baseline Characteristics of the Infant Aphakia Treatment Study Population: Predicting Recognition Acuity at 4.5 Years of Age. *IOVS* 2015; 56:388-395.
28. Weil N, Lambert SR. Comparison of Contact Lens and IOL Correction of Monocular Aphakia During Infancy. *US Ophthalmic Review* 2015;8:21-22.
29. Lenhart PD, Courtright C, Wilson ME, Lewallen S, Taylor DSI, Ventura MC, Bowman R, Woodward L, Ditta LC, Kruger S, Haddad D, El Shakankiri N, Rai SK, Bailey TC, Lambert SR. Global Challenges in the Management of Congenital Cataract: Proceedings of the International Congenital Cataract Symposium held on March 7, 2014 in New York City, New York. *J AAPOS* 2015;19:e1-e8.
30. Lambert SR, Plager DA, Buckley EG, Wilson ME, DuBois L, Drews-Botsch CD, Hartmann EE, Lynn MJ. The Infant Aphakia Treatment Study: Was the high rate of intraoperative and postoperative adverse events in the intraocular lens group preventable? *J AAPOS* 2015;19:101-103.
31. Freedman SF, Lynn MJ, Beck AD, Bothun ED, Orge FH, Lambert SR. Glaucoma-related adverse events in the first five years after unilateral cataract removal in the Infant Aphakia Treatment Study. *JAMA Ophthalmol* In press
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 Identifier: 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.