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

<u>Major</u> 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-conceptional 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 waver 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-conceptional 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. Biomicrosopy 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 iatrogenicly 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 place 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 3months, 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

Powers (diopters)	Increments (diopters)	Diameters (mm)
+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 fluoroscein 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 ACRYSOF 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 reproliferation 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. Biomicrosopy 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) /m^2 . 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/m^2 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 reproliferation 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 intraviteral 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 ß-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 ± 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 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 ± 8% to ± 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 ± 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.

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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 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 1^{st}, 2^{nd}, 3^{rd}, or 4^{th}) 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.