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5 **GLASSES VERSUS OBSERVATION FOR**  
6 **MODERATE HYPEROPIA IN YOUNG**  
7 **CHILDREN (HTS1)**  
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13 **PROTOCOL**  
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17 **Version 3.0**  
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**HYPEROPIA TREATMENT STUDY 1 (HTS1)**  
**Glasses versus Observation for Moderate Hyperopia in Young Children**  
**PROTOCOL AMENDMENT (8-19-13)**

**This amendment provides for the following protocol changes:**

**Protocol Change #1**

Current Protocol

In the current protocol, eligibility is limited to children 12 to <60 months of age with two primary cohorts divided by age (one younger primary cohort of children 12 to <36 months of age and another older primary cohort of children 36 to <60 months of age).

Proposed Change

The age range for eligibility in the older primary cohort will be extended to <72 months; children 60 to <72 months of age will be included in the older primary cohort (section 2.2.1). For eligibility, children 60 to <72 months of age must have age-normal visual acuity of 20/32 or better in both eyes.

Rationale for Change

Expanding the older cohort age group is expected to increase recruitment without compromising the validity of the results, given that there is no evidence that the treatment effect would differ between 36 to <60 month olds and 60 to <72 month olds.

**Protocol Change #2**

Current Protocol

A masked exam is required at every protocol-specified visit. The masked examiner tests ocular alignment, as well as visual acuity and stereoacuity for those subjects old enough to perform them. The masked examiner tests each of these assessments twice, first with correction and then without correction to maintain masking. The masked examiner also performs a retest if the subject shows suspected deterioration on any of the initial masked assessments, regardless of whether or not their poor test results are with their assigned treatment (e.g. observation group subjects are retested when they test poorly with correction; glasses group subjects are retested when they test poorly without correction).

Proposed Change

At interim visits prior to the 36-month primary outcome exam, a masked exam will be required only if unmasked testing in the assigned correction shows suspected deterioration related to strabismus, distance visual acuity, or stereoacuity in a subject who has not had deterioration confirmed by masked exam at a previous visit. The only procedure(s) to be tested by the masked examiner are those specific tests suggesting deterioration. The masked examiner will test each required assessment(s) twice, first with correction and then without correction. The masked examiner will not perform any retests, given that the masked examiner's initial testing (in the appropriate correction status) may serve as confirmation (or not) of the suspected deterioration detected by unmasked testing. If a masked examiner is not available on the same day as the unmasked testing, a separate masked exam will be scheduled within 2 weeks. See changes to sections 3.3.1 and 3.3.2.

No changes related to masking are proposed to the 36-month primary outcome visit--all testing related to the classification of failure (i.e. ocular alignment, visual acuity, and stereoacuity) will continue to be performed by the masked examiner.

#### Rationale for Change

Feedback from participating sites was that the testing burden associated with the current protocol is excessive and that visits take too long to complete, issues which may be contributing to the study's poor recruitment.

Unmasking the initial testing eliminates the second set of testing that was done solely for the purpose of maintaining masking, as well as retesting that is not related to classification of deterioration, thus substantially reducing the testing burden on the site and subject. Given that the study population is children aged 1 to <6 years old, an additional benefit of less testing may be reduced subject fatigue and better attention, particularly for the very young children.

Unmasking the initial testing also eliminates the need for a masked examiner at every follow up visit, given that a masked examiner would now be needed only if the unmasked initial testing suggests deterioration. Reducing the testing burden for the subject may also help retention.

The Steering Committee acknowledges that the proposed change does have a potential disadvantage. The original purpose of the masking was not only to allow unbiased determination of the 3-year failure outcome, but also to allow unbiased determination of deterioration during the study. The classification of deterioration triggers mandatory prescription of glasses in observation group subjects and releases subjects in both groups to further treatment at investigator discretion. The specific concern regarding deterioration is that it could be overcalled in the observation group, resulting in glasses being prescribed earlier than necessary. This situation would make the treatments received in each group more similar and thus bias against finding a treatment group difference in the primary outcome at 3 years.

In the proposed change, the determination of deterioration remains sufficiently masked because the trigger for the masked retest is the unmasked initial testing OR parental concern in the absence of deterioration (see protocol change # 3 below). Therefore, the masked examiner will not know whether or not deterioration was found on unmasked testing and the proposed change should not bias the masked examiner towards finding deterioration. Consequently, the Steering Committee feels that having a confirmatory retest by a masked examiner will be adequately rigorous.

#### **Protocol Change #3**

##### Current Protocol

When a subject first meets deterioration criterion (with the exception of deterioration for parental concern), the criterion met must be retested by the masked examiner.

##### Proposed Change

If a parent indicates significant concern about the child's eyes that would warrant starting treatment in the absence of meeting formal deterioration criteria by unmasked examination; ocular alignment, distance visual acuity, and stereoacuity must be assessed by a masked examiner.

#### Rationale for Change

Requiring such masked exams would keep masked examiners masked to whether there was suspected deterioration on unmasked testing, because under this proposed protocol change a masked

exam would also performed if the parent expressed significant concern about the child's eyes that would warrant starting treatment.

#### **Protocol Change #4**

##### Current Protocol

Deterioration and failure criteria may be met if stereoacuity at near by the Randot Preschool stereotest is below age normal values or has decreased 2 or more octaves ( $\geq 0.6$  log seconds of arc) from the best previously recorded stereoacuity or to nil.

##### Proposed Change

The stereoacuity portion of deterioration and failure will be based solely on whether the stereoacuity is below age normal values, removing the criteria based on whether stereoacuity has decreased 2 or more octaves than the best previously recorded stereoacuity or a drop to nil (sections 3.3.3 and 5.2.1).

##### Rationale for Change

Because the study treatment (refractive correction) may affect stereoacuity, the distribution of best previous stereoacuity may differ between treatment groups, thus compromising the validity of treatment group comparisons based on a change from best stereoacuity.

#### **Protocol Change #5**

##### Current Protocol

The protocol does not address how the analysis will treat cases in which non-protocol treatment is prescribed in the absence of meeting formal deterioration criteria.

##### Proposed Change

Specified that non-protocol treatment for refractive error, amblyopia, and/or ocular alignment prescribed in the absence of meeting formal deterioration criteria (any treatment other than refractive correction in the glasses group or any treatment in the observation group) will be considered deterioration for analysis purposes (sections 3.3.3 and 4.5). Non-protocol treatment has no impact on the primary outcome of failure at 36 months unless strabismus surgery was received, in which case the subject is considered failed.

##### Rationale for Change

Subjects who have not met deterioration criteria but who receive treatment other than their randomized treatment are not at the same risk of deterioration as subjects who have not started such treatment. For example, a subject who was started on amblyopia treatment even though deterioration criteria were not met (e.g. subject was too young to have visual acuity tested or subject's interocular difference did not quite meet deterioration criteria) may be expected to be at less risk of amblyopia than someone who did not receive such treatment.

#### **Protocol Change #6**

##### Current Protocol

Currently, binocular near visual acuity testing at the 36-month primary outcome exam is performed with and without correction by the masked examiner.

##### Proposed Change

Binocular near visual acuity testing may be performed by an unmasked examiner (section 3.6.2).

Rationale for Change

Binocular near visual acuity is a secondary outcome and does not influence whether the subject fails at the 36-month primary outcome visit. To decrease the burden on the subject and the masked examiner, this testing will not be completed during the masked portion of the exam.

**Protocol Change #7**

Current Protocol

Children with any prior refractive correction are ineligible for the study.

Proposed Change

The study will allow prior treatment of refractive correction that was one week or less and occurred more than 2 months prior to enrollment (section 2.2.2)

Rationale for Change

We have precedent in some of our previous amblyopia studies to allow a very minimal amount of prior treatment to essentially count as ‘no treatment.’ We would not expect one week or less of refractive correction to have a meaningful effect, particularly if it occurred more than two months before enrollment.

**This amendment also provides for the following minor protocol changes/clarifications:**

- Clarified that the requirement that the examiner be a study-certified pediatric ophthalmologist, pediatric optometrist, or certified orthoptist pertains only to the ocular alignment testing. Visual acuity and stereoacuity testing may be performed by any masked examiner who is PEDIG-certified to perform the specific assessment (section 3.7).
- Specified that a course of short-term, bilateral cycloplegia to assist in relaxing the subject’s accommodation to adapt to the glasses can now be prescribed at investigator discretion and will not require approval by the protocol chair (see sections 3.1.2 and 3.4) because this is routine practice. If bilateral cycloplegia is prescribed, it must be stopped at least two weeks prior to any study visit. Data regarding how often bilateral cycloplegia is prescribed will be gathered at follow up visits.
- Specified that deterioration can occur at any follow up visit and is not limited to protocol-specified visits (section 3.3.3)
- Clarified procedures for the 36-month primary outcome exam. If a subject meets any failure criteria (with the exception of strabismus surgery prior to the 36-month outcome exam); the visual condition that is considered to be failed must be retested by the masked examiner (*section 3.6.1*). This information was previously located only in the statistical analysis chapter.
- Clarified that for each assessment in the masked exam, both with correction testing and without correction testing should be completed before proceeding to the next assessment (section 3.3.2 and 3.6.1)

- Specified that at interim follow up visits, the subjects current glasses must be verified as correct by lensometry prior to any unmasked testing (section 3.3.1).
- Clarified what refractive correction should be used for testing at interim follow up visits and whether or not deterioration has been confirmed by masked exam previously (section 3.3.1)
- Clarify deterioration criteria (section 3.3.3)
- Clarified what refractive correction should be used for testing at the 36-month primary outcome visit (section 3.6.1)
- Clarified that full cylinder correction refers to both power and axis (sections 1.4, 3.1.2, 3.6.1)
- Specified that atropine is allowed for treatment of amblyopia but must be discontinued at least 2 weeks before the 36-month primary outcome visit (section 4.5)
- Clarified that subjects who have not met deterioration criteria must continue with their randomized treatment assignment (no correction for observation group subjects, hyperopic correction per protocol for glasses group subjects) with no additional treatment (sections 3.1.1 and 3.1.2).
- Habitual correction has been clarified as randomized correction throughout the protocol.
- Clarified the method of payment to the parent for travel reimbursement as by check or by merchandise or money-card (section 4.9)
- Clarified contact information for a change in protocol chairs on cover page

## PROTOCOL AMENDMENT 2 (1-23-15)

**This amendment provides for the following protocol changes:**

### **Protocol Change #1**

#### Current Protocol – section 3.6.1

The appropriate hyperopic correction for testing in trial frames at the 36-month primary outcome exam is based on the cycloplegic refraction at 30 months defined as follows:

- If deterioration has not been confirmed by masked exam at a previous visit, subjects should be tested in partial plus (sphere cut symmetrically by 1.00D, with full cylinder).
- If deterioration has been confirmed by masked exam at a previous visit, subjects should be tested in full sphere and cylinder correction (magnitude and axis)

#### Proposed Change – section 3.6.1

The appropriate hyperopic correction for testing in trial frames at the 36-month primary outcome exam is based on *the most recent* cycloplegic refraction and most recent glasses-correction (if any) defined as follows:

- If deterioration has been confirmed by masked exam at a previous visit, and refractive correction with full plus was prescribed as glasses at the most recent visit, the subject should be tested in trial frames with full sphere and cylinder correction (magnitude and axis) from the most recent cycloplegic refraction
  - *Full plus prescribed at the most recent visit* is defined as prescribed sphere within 0.25D of the cycloplegic refraction
- Otherwise, the subject should be tested in trial frames with partial plus (sphere cut symmetrically by 1.00D, with full cylinder correction magnitude and axis) from the most recent cycloplegic refraction

#### Rationale for Change

The current protocol would require testing in full plus for all subjects who previously deteriorated (regardless of the cause of the deterioration or the current glasses correction). However, full plus is only appropriate for certain conditions (for subjects who have been wearing full plus e.g. subjects who deteriorate due to development of an ET). If a subject who has not been wearing full plus is tested in full plus, reduced distance acuity may be found because the subject may not be able to instantaneously relax into the full plus prescription. Therefore, we are requesting to change the current protocol such that if the subject has deteriorated previously and full plus was prescribed at the last visit, then the subject will be tested at the 36-month visit in full plus. Otherwise the subject will be tested in partial plus. This change will provide the most reasonable assessment of true outcome.

**This amendment also provides for the following minor protocol changes/clarifications:**

- Section 3.6.2 - The criteria for repeat testing 4 weeks following the 36-month visit for subjects suspected of meeting failure criteria with a change in cycloplegic refraction were clarified to make clearer that 1) glasses are prescribed at the 36 month visit and 2) assessments are repeated wearing the new glasses at the repeat outcome visit. Testing without correction does not need to be repeated at the repeat outcome visit.



- 335       • Section 5.2.1 – Clarified that for children that return for a repeat outcome visit, the final  
336       assessment of failure for the study will be based upon the assessments without trial frames at  
337       36 months and the assessments in new glasses 4 weeks later.

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## CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and is funded through a cooperative agreement from the National Eye Institute.

### 1.1 Background

The prevalence of hyperopia was reported in recent population-based studies in 6- to 72-month-old children.<sup>1,2</sup> In white children the prevalence of hyperopia was 31.5% with  $\geq +2.00D$ , 13.2% with  $\geq +3.00D$ , 5.2% with  $\geq +4.00D$ , and 2.4% with  $\geq +5.00D$ . Hyperopia prevalence was lower for African-American children (relative prevalence white to African-American = 1.62; 95% CI 1.52 to 1.74).<sup>1</sup> The prevalence of hyperopia  $\geq +2.00D$  (in the better eye) was slightly higher in Hispanic children (19.6%) than in African American children (15.2%).

Moderate and high hyperopia are associated with the development of strabismus and amblyopia. Atkinson et al<sup>3</sup> found that children with greater than  $+3.50D$  in any meridian at 6 to 8 months of age were 13 times more likely to develop strabismus by 4 years of age and 6 times more likely to have amblyopia, compared to infants with low hyperopia or emmetropia. Similarly, a study by Ingram et al<sup>4</sup> found that the presence of  $+2.50D$  or more of hyperopia at 1 year of age was significantly associated with the development of strabismus and/or amblyopia by 3.5 years of age. The American Academy of Ophthalmology consensus guidelines state that hyperopia of  $\geq +6.00D$  in 0- to 1-year olds;  $\geq +5.00D$  in 1-to 2-year olds; and  $\geq +4.50D$  in 2- to 3-year olds is amblyogenic.<sup>5</sup> A threshold of greater than  $+3.50D$  in any meridian has been suggested as a referral criterion for vision screening.<sup>6</sup>

Nevertheless, the question of whether to prescribe glasses for hyperopia remains controversial.

### 1.2 Rationale for the Study

The primary aims of treatment for asymptomatic moderate and high hyperopia in preschool children are to facilitate the development of normal visual acuity and to prevent the development of esotropia and amblyopia. Treatment consists of optical correction, typically using glasses. For children with high hyperopia ( $\geq +5.00D$ ) and without strabismus or amblyopia, there is general consensus that a correction (usually partial plus) should be prescribed.<sup>7</sup> Nevertheless, for children with moderate hyperopia ( $+3.00D$  to  $+5.00D$ ) without strabismus or amblyopia, there is less consensus among pediatric eye care professionals. A survey by Lyons et al<sup>7</sup> found that for a 2-year-old child with hyperopia greater than  $+3.00D$ , 65% of optometrists would prescribe glasses compared to 25% of ophthalmologists; for a 4-year old with hyperopia greater than  $+3.00D$ , 67% of optometrists would prescribe compared with 42% of ophthalmologists. The American Association for Pediatric Ophthalmology and Strabismus (AAPOS) recommends correcting  $+4.00D$  or more in 2 to 7 year olds<sup>8</sup> and the American Academy of Ophthalmology recommends a threshold of  $+4.50D$  for correction in 2-to 3-year olds.<sup>5</sup> Unlike ophthalmology, optometry does not provide specific recommendations based on age and level of refractive error.<sup>9</sup> Such variation in practice highlights the lack of rigorously collected scientific evidence for the management of this condition. Across all levels of hyperopia, most ophthalmologists and optometrists usually prescribe less than the full cycloplegic refraction (71% in the Lyons survey) when no strabismus or amblyopia is present.<sup>7</sup>

The rationale for proactively correcting moderate hyperopia in an asymptomatic child is the prevention of esotropia, amblyopia<sup>3,4</sup> or asthenopia. The argument against correcting moderate hyperopia in an asymptomatic child is the expense and inconvenience of glasses that might be

unnecessary and the potential disruption of emmetropization in infants and toddlers. At present, it remains uncertain whether correction of moderate hyperopia is beneficial in terms of visual acuity outcomes or strabismus development. There is some evidence that using partial correction of hyperopia allows emmetropization to take place.<sup>10</sup>

There are some previous data comparing no spectacle correction of moderate hyperopia to partial correction. Ingram et al<sup>11</sup> randomized 6-month-old children (n=372) with +4.00D or more of hyperopia to glasses or no glasses and found no difference in the rate of strabismus development (23.5% vs. 26% respectively) by 3.5 years of age. Nevertheless, there was a difference in visual acuity outcome between groups: 97% of the glasses group achieved 20/40 or better compared to 87% in the non-glasses group. A study by Atkinson et al<sup>12</sup> allocated infants with +3.50D or more of hyperopia to glasses or no glasses and, in contrast with the Ingram study,<sup>11</sup> found that there was a significant difference in the rate of strabismus development (6.3% vs. 21% respectively). Atkinson et al also found that the rate of amblyopia was lower in the glasses group compared to the non-glasses group (28.6% vs. 68% respectively). In a second study by the Atkinson group,<sup>13</sup> the strabismus findings were not replicated (no difference in rate of strabismus development between glasses [n=58] and non-glasses wearers [n=18]) whereas the visual acuity outcomes were replicated (amblyopia was found in 17% of children in glasses group and 67% of children in non-glasses group).<sup>13</sup> There is unfortunately a lack of standardization in these previous studies, especially regarding visual acuity testing methods. In addition, it is not always clear how amblyopia was defined and whether visual acuity was assessed with or without hyperopic correction (in no-spectacles patients). Furthermore, some reported outcomes include data only for subjects considered to be 'compliant' with glasses.

If refractive correction of moderate hyperopia does not reduce the incidence of amblyopia and/or esotropia compared to no refractive correction, then glasses can be avoided. However, if correcting moderate hyperopia does reduce the development of amblyopia and/or esotropia, then the benefits of preemptive refractive correction will have been identified.

### 1.3 Study Objectives

To compare visual acuity outcomes and development of strabismus after a 3-year follow-up period in children age 12 to <72 months with moderate hyperopia (spherical equivalent +3.00D to +6.00D) who are prescribed glasses either immediately or only after confirmation of pre-specified deterioration criteria.

### 1.4 Synopsis of Study Design

Major eligibility criteria: (See *section 2.2* for a complete listing)

- Age 12 to <72 months
  - The study will consist of two primary cohorts divided by age. One primary cohort will consist of children 12 to <36 months of age and another primary cohort will consist of children 36 to <72 months of age.
- Cycloplegic refraction:
  - +3.00D to +6.00D of spherical equivalent (SE) in either eye
  - Astigmatism  $\leq 1.50$ D in both eyes
  - Spherical equivalent anisometropia  $\leq +1.50$ D
- No prior treatment for refractive error with glasses or contacts (unless treatment was one week or less in duration and occurred more than 2 months prior to enrollment)

- No prior treatment for amblyopia or strabismus (e.g., surgery, patching, vision therapy, etc.)
- No measurable heterotropia at distance (3 meters) or at near (1/3 meter) by cover/uncover testing
- No known neurological anomalies (e.g. cerebral palsy, Down syndrome)
- For children 36 to <72 months of age:
  - No evidence of subnormal visual acuity - Uncorrected monocular visual acuity in both eyes of 20/50 or better for age 36 to <48 months, 20/40 or better for age 48 to <60 months, and 20/32 or better for ages 60 to <72 months measured without cycloplegia using the ATS-HOTV<sup>®</sup> visual acuity testing protocol
  - Zero (0) or 1 logMAR line interocular difference (IOD) in uncorrected visual acuity measured without cycloplegia using the ATS-HOTV<sup>®</sup> visual acuity testing protocol
  - Age-normal stereoacuity on the Randot Preschool Stereotest (*see Table 2*)

#### Primary Cohorts

- One primary cohort consists of patients aged 12 to <36 months.
- A second primary cohort consists of patients aged 36 to <72 months.

#### Treatment Groups

For each primary cohort, patients will be randomized (1:1) to either:

- Observation: glasses will not be prescribed unless the patient has confirmation of one or more deterioration criteria (defined in *section 3.3.3.3*)
- Glasses: glasses are prescribed at enrollment and worn per protocol throughout the duration of the study (unless the glasses correction decreases to +1.00D SE or less during follow-up; then glasses are at investigator discretion)

For patients in the glasses group, the sphere will be cut symmetrically by 1.00D (partial plus) and the full cylinder (magnitude and axis) will be prescribed. Patients in either group who have confirmation of one or more deterioration criteria (defined in *section 3.3.3.3*) will be prescribed glasses with amount of sphere and cylinder correction according to guidelines suggested in *section 3.4*.

#### Sample Size

The study will enroll 336 patients aged 12 to <36 months and 336 patients aged 36 to <72 months in the primary cohorts.

#### Visit Schedule (timed from randomization)

- Enrollment exam
- 6 months  $\pm$  1 month
- 12 months  $\pm$  1 month
- 18 months  $\pm$  1 month
- 24 months  $\pm$  1 month
- 30 months  $\pm$  1 month
- 36 months  $\pm$  1 month
- Repeat 36-month outcome exam within 4 weeks for subjects meeting failure criteria (*section 5.2*) and requiring change in glasses (*section 4.3*).

At each 6-month follow-up visit, monocular distance visual acuity using the ATS-HOTV (if old enough to perform), cover uncover test, simultaneous prism cover test (SPCT) (if deviation present), prism and alternate cover test (PACT), the Randot Preschool Stereoacuity test (if old enough to perform), and dynamic retinoscopy (optional) will be performed. Near visual acuity will be tested at 36 months.

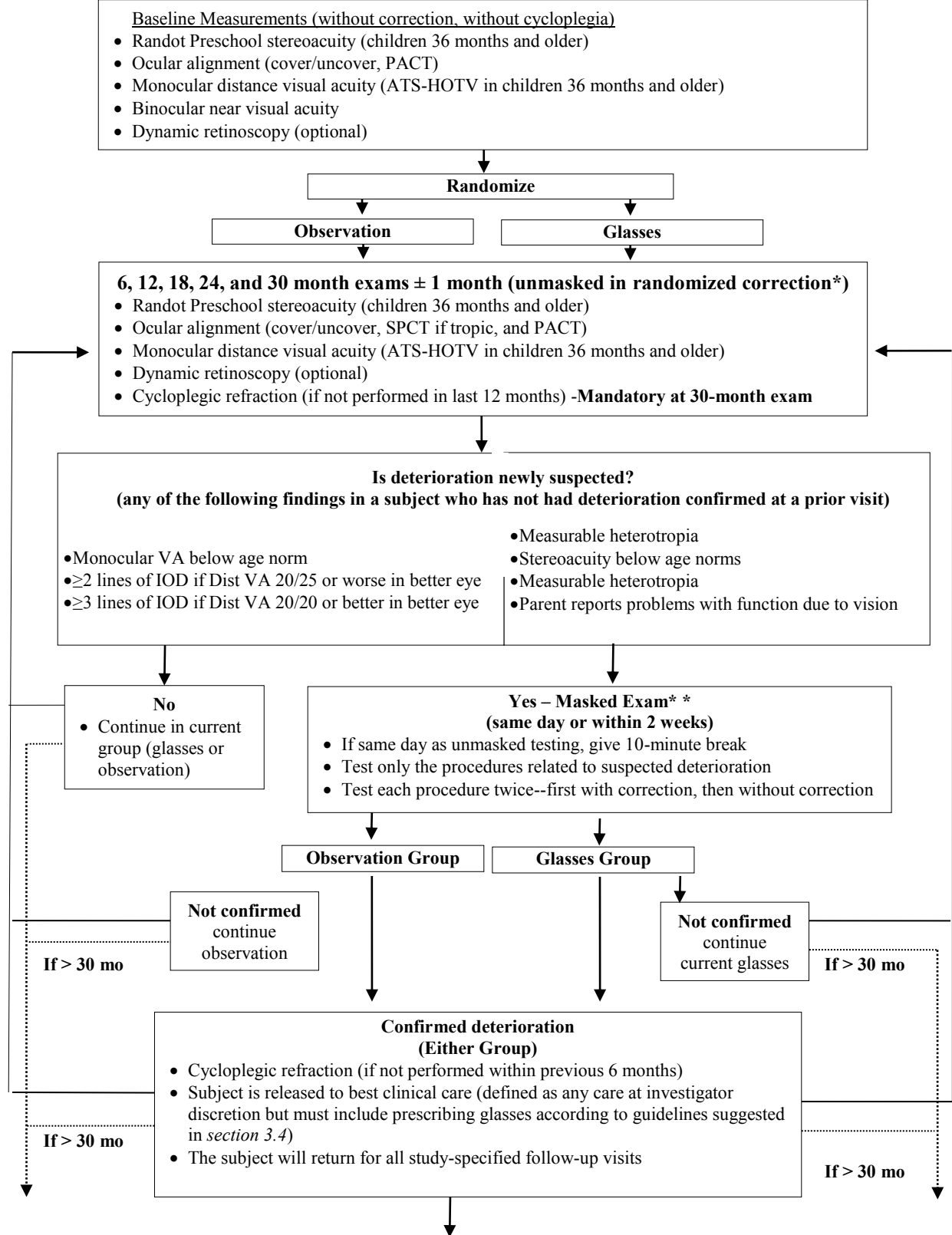
The primary outcome exam will be 36 months after randomization. Cycloplegic refraction will be performed yearly (or more frequently if clinically indicated); a mandatory cycloplegic refraction will be performed at the 30-month follow-up visit and again at the 36-month outcome exam. Subjects meeting failure criteria and requiring a change in glasses at the 36-month outcome exam will return for a repeat outcome exam in the updated glasses within 4 weeks.

#### Primary Analysis

For each of the two primary cohorts, the proportion meeting failure criteria at 3 years post-randomization will be compared between treatment groups using the Fisher's exact test.

- Failure (confirmed by a retest at the same visit) will be determined at the 36-month primary outcome visit and is defined in *section 5.2.1*.

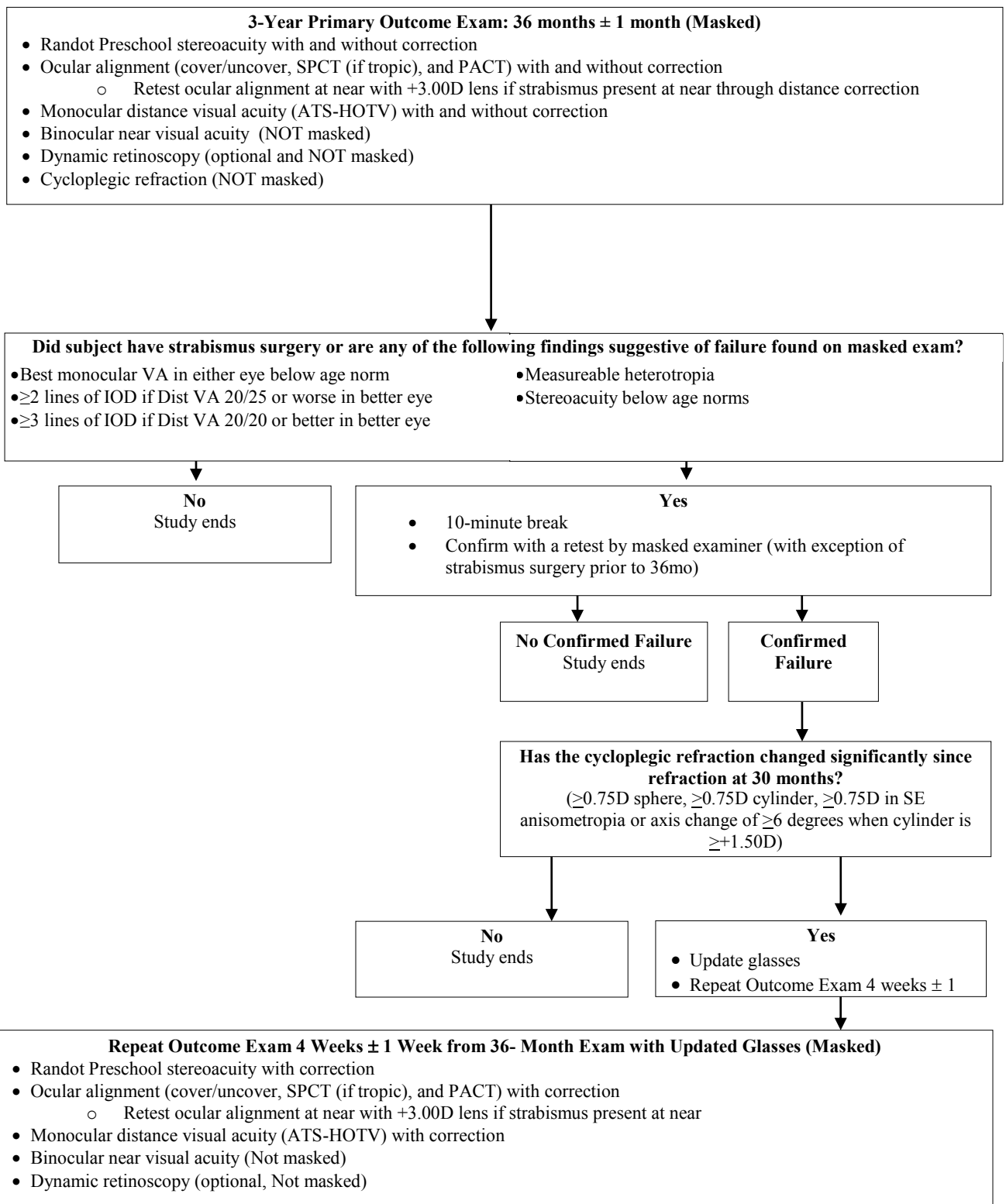
565     **Study Summary Flow Chart**



\* Testing is performed in child’s glasses and no masked exam is needed at interim follow up visits for children who have previously been classified as deteriorated

\*\* - Unless site is pre-authorized for non-masked 6-12, 18, 24, and 30 month visits in which case retest is performed by non-masked personnel.





## CHAPTER 2: PATIENT ENROLLMENT

### 2.1 Eligibility Assessment and Informed Consent

The study will enroll a minimum of 336 subjects for the primary cohort of patients aged 12 to <36 months at enrollment, and a minimum of 336 subjects for a separate primary cohort of patients aged 36 to <72 months at enrollment. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded.

A patient is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard of care), or a referral, that identifies hyperopia that appears to meet the eligibility criteria. The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)). Parent(s) who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the parent prior to performing any study-specific procedures that are not part of the patient's routine care.

### 2.2 Eligibility and Exclusion Criteria

#### 2.2.1 Eligibility Criteria

The following criteria must be met for the patient to be enrolled in the study:

1. Age 12 to <72 months
2. Refractive error between +3.00D and +6.00D SE (by cycloplegic refraction) in either eye
3. Astigmatism  $\leq 1.50D$  in both eyes
4. Spherical equivalent anisometropia  $\leq +1.50D$
5. For children 36 to <72 months of age:
  - a. Normal visual acuity for age - Uncorrected monocular visual acuity in both eyes using the ATS-HOTV<sup>®</sup> visual acuity testing protocol without cycloplegia (*see section 3.3.3, Table 1*)
  - b. No amblyopia - Zero (0) or 1 logMAR line interocular difference (IOD) in uncorrected visual acuity without cycloplegia using the ATS-HOTV<sup>®</sup> visual acuity testing protocol
  - c. Normal near stereoacuity for age using the Randot Preschool Stereoacuity test (*see section 3.3.3, Table 2*)
6. Gestational age  $\geq 32$  weeks
7. Investigator is willing to prescribe glasses per protocol or observe the hyperopia untreated for 3 years unless specific criteria for deterioration outlined in *section 3.3.3* are confirmed.
8. Parent understands the protocol and is willing to accept randomization to either glasses or no glasses initially, and is willing to wear glasses as prescribed or accept that glasses will not be prescribed by the investigator unless specific deterioration criteria outlined in *section 3.3.3* are confirmed.
9. Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff.
10. Relocation outside of area of an active PEDIG site for this study within the next 36 months is not anticipated.

#### 2.2.2 Exclusion Criteria

A patient is excluded for any of the following reasons:

1. Any measurable heterotropia at distance (3 meters) or at near (1/3 meter) by cover/uncover testing. Note that patients with heterophoria are eligible.
2. Previous documented strabismus (parental report must be confirmed by investigator)
3. Manifest or latent nystagmus evident clinically

4. Previous treatment of refractive error with glasses or contacts unless duration of glasses or contacts wear was one week or less and occurred more than 2 months prior to enrollment.
5. Previous intraocular, refractive, or extraocular muscle surgery
6. Previous amblyopia treatment
7. Previous vergence/accommodative therapy
8. Parental concerns over learning or development
9. Ocular co-morbidity that may reduce visual acuity
10. Symptoms of blur or asthenopia
11. Developmental delay diagnosed by pediatrician or Individualized Education Program (IEP)
12. Known neurological anomalies (e.g. cerebral palsy, Down syndrome)
13. Inability to perform visual acuity ATS-HOTV testing if  $\geq 36$  months of age

### 2.3 Historical Information

Historical information to be elicited will include the following: date of birth, gender, race, ethnicity, reason for coming for exam, history of prior eye-related treatment, and diagnosis and current treatment of ADHD. Family history of strabismus and/or amblyopia, patching, or glasses before the age of 7 years will also be collected.

### 2.4 Procedures at the Enrollment Visit

All examination procedures must be tested within 14 days prior to enrollment, except a cycloplegic refraction, which must be tested within 2 months prior to enrollment. All examination procedures at enrollment are performed without correction and without cycloplegia in the following order:

1. Stereoacuity Testing (patients  $\geq 36$  months of age only):

  - Stereoacuity will be tested at near without correction using the Randot Preschool Stereoacuity test.

2. Ocular Alignment Testing:
  - Ocular alignment will be assessed without correction by the cover/uncover test and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter) as outlined in the *Hyperopia Testing Procedures Manual*.
    - See *section 2.2.1* for eligibility criteria related to ocular alignment.
  - A parental report of strabismus must be confirmed by clinical testing performed by the investigator. If the investigator fails to find strabismus, the subject may be brought back at investigator discretion. If the return visit is within two weeks, other clinical measures made within 14 days of this repeated ocular alignment testing may be used for enrollment.
3. Distance Visual Acuity Testing (patients  $\geq 36$  months of age only): Monocular distance visual acuity testing will be performed without correction in each eye by a certified examiner using the ATS single-surround HOTV protocol on a study-certified acuity tester as described in the *ATS Testing Procedures Manual*. ATS single-surround HOTV protocol will be used throughout the study.
  - No visual acuity data (including fixation preference) will be collected on children  $<36$  months old.
  - Testing must be completed without cycloplegia.
  - At investigator discretion acuity may be retested on the same day or subsequent day to assess eligibility.

4. Binocular Near Visual Acuity Testing (patients  $\geq 36$  months only): Binocular near visual acuity testing will be performed without correction as described in the *Hyperopia Study Testing Procedures Manual*.
5. Additional Clinical Testing:
- Undilated dynamic retinoscopy (optional) at near without correction as outlined in the *Hyperopia Testing Procedures Manual*.
  - Ocular examination as per investigator's clinical routine (if not performed within 6 months)
  - Cycloplegic refraction (if not performed within 2 months) using drops containing cyclopentolate (must achieve stable retinoscopy reflex)
    - See *section 2.2.1* for eligibility criteria for refractive error

## **2.5 Randomization of Eligible Patients**

The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by primary cohort (age 12 to <36 months and age 36 to <72 months) and by site which will specify the order of treatment group assignments. All eligible patients enrolled in the study will be randomized to one of the following groups:

1. Observation: glasses not prescribed unless confirmation of one or more deterioration criteria
2. Glasses: glasses prescribed immediately

Patients will be randomized in a 1:1 ratio.

Once a patient is randomized, that subject will be included in the analysis regardless of whether the assigned treatment is received or not. They will also remain in the study and return for the protocol-specified follow-up visits. Thus, the investigator must not randomize a patient until he/she is convinced that the parent will accept either of the treatment groups.

Parents of children randomized to glasses should be encouraged to fill the glasses prescription as soon as possible following randomization but glasses must begin within 30 days of randomization.

## CHAPTER 3: TREATMENT AND FOLLOW-UP

### 3.1 Treatment

#### 3.1.1 Observation Group

Subjects randomized to the observation group will receive no glasses to correct the child's refractive error or any other treatment unless one or more deterioration criteria are confirmed.

If a subject meets deterioration criteria (section 3.3.3) at any visit, the subject will then be released to best clinical care, which is defined as care at the investigator's discretion, but must include prescribing glasses according to guidelines suggested in *section 3.4*. The subject will return for all study-specified follow-up visits, including masked examination at the 36-month primary outcome exam.

If a subject does not meet deterioration criteria, the subject will continue to be observed without glasses or any other treatment for amblyopia and ocular alignment, and will return for all study-specified follow-up visits.

#### 3.1.2 Glasses Group

Subjects randomized to the glasses group will receive partial plus glasses, i.e., with sphere cut symmetrically by 1.00D (from a cycloplegic refraction within 2 months prior to enrollment) and full cylinder correction (magnitude and axis). Unmasked personnel at the site (e.g. site investigator or coordinator) will directly contact the parents of each participant who is assigned to glasses treatment within the first 2 weeks of the study to inquire about any issues with obtaining glasses and to encourage treatment compliance.

If the investigator feels that the subject is not compliant with wearing his/her glasses and/or needs assistance relaxing his/her accommodation to adapt to the glasses, the investigator is encouraged to prescribe a short course of bilateral cycloplegia. If bilateral cycloplegia is prescribed, it must be stopped at least two weeks prior to any study visit.

If a subject meets deterioration criteria (section 3.3.3) at any visit, the subject will then be released to best clinical care, which is defined as care at the investigator's discretion, but must include continued use of glasses according to guidelines suggested in *section 3.4*. The subject will return for all study-specified follow-up visits, including masked examination at the 36-month primary outcome exam.

If a subject does not meet deterioration criteria, the subject will continue treatment with glasses only (any other treatment for amblyopia or ocular alignment is prohibited) and return for all study-specified follow up visits.

Subjects in the glasses group will continue to wear glasses throughout the study unless the glasses correction decreases to +1.00D spherical equivalent (SE) or less (then glasses may be discontinued at investigator's discretion).

### 3.2 Follow-up Visit Schedule

The follow-up schedule is timed from randomization as follows:

- 6-month: 6 months  $\pm$  1 month
- 12-month: 12 months  $\pm$  1 month
- 18-month: 18 months  $\pm$  1 month
- 24-month: 24 months  $\pm$  1 month

- 30-month: 30 months  $\pm$  1 month
- 36-month: 36 months  $\pm$  1 month (masked primary outcome examination)
  - Repeat 36-month outcome exam 4 weeks  $\pm$  1 week for subjects meeting failure criteria (*section 5.2*) and requiring change in glasses (*section 4.3*).

If unmasked testing at any visit before 36 months shows suspected deterioration related to strabismus, distance visual acuity, stereoacuity, or parental concern (*section 3.3.3*), and the subject has not had deterioration confirmed at a previous visit, a separate masked exam (*section 3.3.2*) must be completed within 2 weeks if it cannot be completed on the same day as the unmasked testing.

Additional non-specified visits can be performed at the discretion of the investigator; however, the decision to schedule non-specified visits may not be based on group assignment (e.g., additional non-specified visits cannot be routinely scheduled for subjects in the observation group but not the glasses group).

### **3.3 Follow-up Visits at 6, 12, 18, 24, and 30 months**

Subjects will be seen every 6 months  $\pm$  1 month as outlined in *section 3.2*.

#### **3.3.1 Unmasked Exam**

Each protocol-specified visit between 6 and 30 months will have an unmasked exam.

Prior to performing any testing, unmasked personnel will verify the current glasses prescription using a lensometer.

The testing procedures below should be performed as follows:

- If deterioration has not been confirmed by masked exam at a previous visit, subjects should be tested in randomized correction.
  - Subjects in the observation group will be tested with no refractive correction.
  - Subjects in the glasses group will be tested in appropriate hyperopic correction. The subject's current glasses may be worn for testing provided lensometry completed prior to testing verifies that the plus cut symmetrically by +1.00D based on most recent cycloplegic refraction, otherwise, trial frames should be used.
- If deterioration has been confirmed by masked exam at a previous visit:
  - Subjects will be tested in their current refractive correction.

Note: for subjects wearing bifocals, only the appropriate distance correction will be placed in the trial frame.

The following procedures should be performed by an unmasked examiner in the following order at each visit:

#### **1. Stereoacuity Testing (subjects $\geq$ 36 months only):**

- Stereoacuity will be tested using the Randot Preschool Stereoacuity test at near (1/3 meter).

#### **2. Ocular Alignment Testing:**

- Ocular alignment will be assessed using cover/uncover, SPCT (if tropia is present and of sufficient duration to measure), and PACT, both in primary gaze at distance (3 meters) and at near (1/3 meter).

796 3. Distance Visual Acuity Testing (subjects  $\geq$  36 months only):

- 797 • Monocular visual acuity testing at all follow-up exams will be done without cycloplegia  
798 using the ATS single-surround HOTV letter protocol on study-certified visual acuity  
799 system.

801 4. Cycloplegic Refraction (see section 2.4):

- 802 • A mandatory cycloplegic refraction will be performed at the 30-month follow-up visit,  
803 even if cycloplegia has been performed within the past 12 months.
- 804 • A cycloplegic refraction will be performed at all other follow-up exams if not  
805 performed within the last 12 months. If a new deterioration criterion is confirmed,  
806 cycloplegic refraction must be performed if one has not been done within the past 6  
807 months.
- 808 • If a cycloplegic refraction is performed, it will be performed only after all clinical  
809 testing listed (including any retests if deterioration criteria are met (section 3.3.3)) is  
810 completed.

811 5. Other Testing/Data Collection:

- 813 • Dynamic retinoscopy (optional) at near is performed as outlined in the *Hyperopia*  
814 *Testing Procedures Manual*. *This must be done without cycloplegia*.
- 815 • At each visit, data will be collected on glasses wear compliance based on interviews with  
816 the parent and child.
- 817 • At each visit, parents will be asked if they have concerns about their child's vision,  
818 asking, "Do you have concerns with your child's vision or ability to see well close up?"
- 819 • History of diagnosis of ADHD and the use of medications associated with the disorder  
820 will be elicited and recorded at each follow-up visit.
- 821 • History of use of bilateral cycloplegia in children assigned to glasses will be elicited and  
822 recorded at each follow-up visit.

823

824 If unmasked testing shows suspected deterioration related to strabismus, distance visual acuity,  
825 stereoacuity, or parental concern (section 3.3.3), and the subject has not had deterioration confirmed  
826 at a previous visit, a masked exam (section 3.3.2) must be completed either the same day or within 2  
827 weeks. If a child  $\geq$ 36 months of age shows no deterioration related to strabismus but is unable to  
828 perform distance visual acuity and/or stereoacuity testing, the investigator may, at their discretion,  
829 attempt to repeat testing on the same day or continue in follow-up until the next protocol specified  
830 follow-up visit.

831 **3.3.2 Masked Exams for Subjects with Newly Suspected Deterioration**

832 A masked exam is required if unmasked testing shows suspected deterioration related to strabismus,  
833 distance visual acuity, stereoacuity, or parent concern (section 3.3.3), and the subject has not  
834 already had deterioration confirmed at a previous visit. The masked exam should be completed  
835 either the same day as the unmasked testing (after a 10-minute break) or within 2 weeks.

836

837 Because the masked examiner must be masked to the subject's treatment group, he/she must be  
838 someone other than the treating investigator.

839

840 The only procedure(s) to be tested by the masked examiner are those which relate to the visual  
841 condition with suspected deterioration (section 3.3.3). If parental concern is expressed that would  
842 warrant starting treatment in the absence of suspected deterioration by unmasked examination;  
843 ocular alignment, distance visual acuity (if  $\geq$ 36 months old), and stereoacuity (if  $\geq$ 36 months old)  
844 must be assessed by the masked examiner.

Unmasked personnel will specify on the masked exam worksheet what assessment(s) the masked examiner needs to test.

All required procedures will be performed twice to facilitate masking, first with appropriate hyperopic correction in trial frames and second without correction. Appropriate hyperopic correction is defined as follows:

- Refractive correction in which the plus is cut symmetrically by +1.00D based on most recent cycloplegic refraction.

For each assessment, the testing with correction and testing without correction should be completed before proceeding to the next assessment.

The trial frame lenses must be placed in the trial frame by someone other than the masked examiner and the trial frame must be placed on the subject before the masked examiner enters the room. Prior to the masked examiner entering the room, subjects and parents should be instructed not to discuss their treatment with the masked examiner.

The unmasked investigator will review the findings from the masked testing to determine if one or more deterioration criteria were confirmed. Deterioration is confirmed if one or more deterioration criteria below (section 3.3.3) are met.

### **3.3.3 Deterioration Criteria**

A subject's condition will be considered to have deteriorated if any of the following criteria are met during testing while wearing their randomized correction\* at any protocol-specified or unspecified visit after randomization, based on unmasked testing (3.3.1) and **confirmed** by a retest performed by a masked examiner (section 3.3.2).

1. Strabismus -any measurable heterotropia detected by a cover/uncover test in primary gaze at distance (3 meters) or at near (1/3 meter) in the randomized correction
2. Distance visual acuity meeting any of the following criteria:
  - Distance visual acuity below age normal values in either eye (*see Table 1*)
  - $\geq 2$  logMAR lines of IOD if visual acuity is 20/25 or worse in the better eye
  - $\geq 3$  logMAR lines of IOD if visual acuity is 20/20 or better in the better eye
3. Stereoacuity in randomized correction at near by the Randot Preschool stereotest below age normal values (*see Table 2*).
4. Investigator determines that the parent has significant concern about the child's eyes that would warrant starting treatment in the absence of meeting formal deterioration criteria (after discussing any concerns raised with the parent). In the case of parental concern, the patient will be classified as deteriorated if the parental concern persists and non-protocol treatment is begun regardless of the results of the masked examination.

\*Randomized correction is defined as follows:

- No refractive correction for subjects in the observation group.
- Appropriate hyperopic correction for subjects in the glasses group. Appropriate hyperopic correction is that in which the plus is cut symmetrically by +1.00D based on most recent cycloplegic refraction.



For analysis, subjects will also be classified as deteriorated if for any reason non-protocol treatment is prescribed AND received without first meeting one of the deterioration criteria above. Non-protocol treatment includes any treatment for refractive error, amblyopia, and/or ocular alignment other than refractive correction in the glasses group or any treatment in the observation group. Increasing plus (including prescribing full plus) for subjects in the glasses group is not considered non-protocol treatment and will not be considered deterioration.

Table 1: Normal Visual Acuity Values Based on Age (ATS-HOTV)

Age range	Subnormal if worse than
36-47 months	20/50
48-59 months	20/40
60-83 months	20/32
≥84 months	20/25

Normal values for children aged 30-72 months based on a study by Pan et al.<sup>14</sup> Normal values for children aged ≥72 months based on a study by Drover et al.<sup>15</sup>

Table 2: Normal Randot Preschool Stereoacuity Values at Near Based on Age

Age range	Subnormal if worse than (arcsec)
3 years	400"
4 years	200"
5 years	200"
6 years	100"
7 years	60"
8+ years	60"

Normal values based on Birch et al.<sup>16</sup>

### 3.3.4 Pre-Approved Unmasked Sites

Prior to the start of the study, the Hyperopia Treatment Study Steering Committee will determine sites that will be authorized to perform non-masked exams at 6, 12, 18, 24, and 30 month visits. Unlike at the masked sites, confirmatory retesting for suspected deterioration at these visits will be performed by an examiner unmasked to treatment group. The 36-month outcome exam will continue to be masked for all subjects at all sites (see *section 3.6*).

## 3.4 Post-Deterioration Glasses Treatment

All subjects with confirmation of one or more deterioration criteria (section 3.3.3) prior to the 36-month outcome visit will be provided refractive correction and continue to return for additional follow-up at the study-specified 6-month intervals. All subjects with confirmation of one or more deterioration criteria must be treated with glasses; correction with contact lenses is not allowed. The amount of sphere and cylinder to prescribe is at investigator discretion, but should follow the guidelines suggested in *Table 4*. Additional treatment and management is at investigator discretion and may include (but is not limited to): lenses, prism, surgery, amblyopia treatment, bifocals, and vergence/accommodative therapy. The prescription of prisms and bifocals is at investigator discretion.

Table 4: Guidelines for Post-Deterioration Glasses Prescription

Hypermetropia should not be undercorrected by more than +1.00D spherical equivalent
Reduction in plus sphere should be symmetric in the two eyes
Cylinder power in both eyes should be within 0.50D of fully correcting the astigmatism
Cylinder axis in the spectacle lenses in both eyes should be within 6 degrees of the axis of the cycloplegic refraction when cylinder power is >1.00D
If a patient develops an ET, he or she should be given a trial of full plus

If the calculated glasses correction is +1.00D SE or less, prescribing glasses is at the investigator's discretion.

If the investigator feels that the subject is not compliant with wearing his/her glasses and needs assistance relaxing his/her accommodation, the investigator is encouraged to prescribe bilateral cycloplegia. If bilateral cycloplegia is prescribed, it must be stopped at least two weeks prior to the 36-month primary outcome exam.

### 3.5 30-Month Follow-up Visit

Subjects will be seen 30 months  $\pm$  1 month from enrollment. The exam will follow all procedures as outlined in *section 3.3*. Each participant will receive a mandatory cycloplegic refraction (*section 2.4*), even if a cycloplegic refraction has been performed within the prior 12 months, and glasses will be updated if refractive error meets the criteria outlined in *section 4.3*.

### 3.6 36-Month Primary Outcome Exam

Subjects will be seen 36 months  $\pm$  1 month from enrollment. Subjects will be seen first by a masked examiner who will complete outcome-related testing including any required retests (*section 3.6.1*), then will have unmasked testing performed (*section 3.6.2*).

#### 3.6.1 Masked Exam

All required procedures will be performed twice to facilitate masking, first with appropriate hyperopic correction in trial frames and second without correction. The appropriate hyperopic correction for testing in trial frames at the 36-month primary outcome exam is based on *the most recent cycloplegic refraction and most recent glasses-correction (if any)* defined as follows:

- If deterioration has been confirmed by masked exam at a previous visit, *and refractive correction with full plus was prescribed as glasses at the most recent visit*, the subject should be tested in trial frames with full sphere and cylinder correction (magnitude and axis) from the most recent cycloplegic refraction
  - *Full plus prescribed at the most recent visit* is defined as prescribed sphere within 0.25D of the cycloplegic refraction
- Otherwise, the subject should be tested in trial frames with partial plus (sphere cut symmetrically by 1.00D, with full cylinder correction magnitude and axis) from the most recent cycloplegic refraction

For subjects wearing bifocals at the time of the masked outcome exam, only the appropriate distance correction will be placed in the trial frame. All trial frame lenses must be placed in the trial

frame by someone other than the masked examiner and the trial frame should be placed on the subject before the masked examiner enters the room.

The following procedures will be performed in the specified order at the 36-month masked outcome exam according to the procedures as outlined in *section 3.3*.

1. Stereoacuity Testing: (masked)

- Stereoacuity will be tested at near (1/3 meter) with distance correction placed in a trial frame and then without correction using the Randot Preschool Stereoacuity test.

2. Ocular Alignment Testing: (masked)

- Ocular alignment will be assessed using cover/uncover, SPCT (if a tropia is present and of sufficient duration to measure), and PACT, both in primary gaze at distance (3 meters) and at near (1/3 meter), with distance correction placed in a trial frame and then without correction.
- If a subject has a measureable heterotropia at near in his/her distance correction, +3.00D lenses OD/OS will be added to the trial frames and the subject's ocular alignment at near will be retested.

3. Distance Visual Acuity: (masked) by ATS-HOTV: Monocular visual acuity testing at the 36-month outcome exam will be done without cycloplegia by a certified examiner using the ATS single-surround HOTV letter protocol on a study-certified visual acuity system. Distance visual acuity will be measured both with correction placed in a trial frame and without correction.

For each assessment, the testing with correction and testing without correction should be completed before proceeding to the next assessment.

If a subject meets any failure criteria (section 5.2.1) with the exception of strabismus surgery prior to the 36-month outcome exam, the visual condition that is considered to be failed must be retested by the masked examiner after a 10 minute break.

- If suspected failure relates to strabismus, ocular alignment will be assessed using the cover/uncover test in primary gaze at distance (3 meters) and/or at near (1/3 meter).
- If suspected failure relates to distance visual acuity, monocular visual acuity testing at will be tested without cycloplegia using the ATS single-surround HOTV letter protocol on study-certified visual acuity system.
- If suspected failure relates to stereoacuity, stereoacuity will be tested using the Randot Preschool Stereoacuity test at near (1/3 meter).

### **3.6.2 Unmasked Exam**

Following the masked exam, the following procedures will be assessed by an unmasked examiner in the same correction used for masked testing as described in 3.6.1:

1. Binocular Near Visual Acuity Testing:

- Binocular near visual acuity will be performed as described in the *Hyperopia Testing Procedures Manual*.

2. Other Testing/Data Collection:

- Undilated dynamic retinoscopy (optional) at near will be performed as outlined in the *Hyperopia Testing Procedures Manual*.
- Data will be collected on glasses wear compliance based on interviews with the parent and child
- History of diagnosis of ADHD and the current use of medications associated with the disorder will be elicited and recorded.

### 3. Cycloplegic Refraction:

- A cycloplegic refraction (*Section 2.4*) will be performed only after all clinical testing listed (including any retests if one or more failure criteria are met (*section 5.2*)) is completed.
- If the subject meets any failure criteria\* with the exception of strabismus surgery prior to the 36-month outcome exam AND the cycloplegic refraction is significantly different from the cycloplegic refraction used to determine the correction used for testing (*section 4.3*), a new refractive correction should be prescribed according to the guidelines in Section 3.4, Table 4. The subject will return 4 weeks  $\pm$  1 week later and all tests performed at the 36-month outcome exam will be repeated with the child wearing their new glasses (testing without correction to facilitate masking does NOT need to be repeated).
  - \* Failure criteria met for strabismus, visual acuity, or stereoacuity as defined in 5.2.1 BOTH with and without trial frames for that criterion

### 3.7 Examiner Qualifications

Examiner qualifications are as follows:

- Ocular alignment must be assessed by a study-certified pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
- Visual acuity and stereoacuity testing can be performed by any examiner who is PEDIG certified to perform the specific assessment.

Unmasked testing can be performed by the investigator or by any other examiner who meets the above criteria. Because the masked examiner must be masked to the subject's treatment group, he/she must be someone other than the treating investigator, who is masked to treatment group and meets the criteria above.

### 3.8 Non-Study Visits and Treatment

Investigators may schedule additional visits at their own discretion. Subjects will continue to follow the study-specified follow-up schedule regardless of any non-study visits.

Investigators must not start any additional treatment (other than that outlined in *section 3.1*) prior to the 36-month outcome visit unless one or more deterioration criteria (*section 3.3.3*) have been met and confirmed by the masked examiner.

## CHAPTER 4: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

### 4.1 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent's contact information. The Jaeb Center will contact the parents of the participants only when necessary. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the participant and/or family and to help coordinate scheduling of the outcome examinations.

The site investigator or coordinator will directly contact the parents of each participant who is assigned to glasses treatment within the first 2 weeks of the study to inquire about any issues with obtaining glasses and to encourage treatment compliance.

### 4.2 Patient Withdrawals

Parents may withdraw their child from the study at any time. This is expected to be a very infrequent occurrence in view of the study design's similarity to routine clinical practice. If the parents indicate that they want to withdraw their child from the study, the investigator personally should attempt to speak with them to determine the reason. If their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the participant in the study under the new provider's care.

### 4.3 Management of Refractive Error

A cycloplegic refraction should be performed every 12 months during follow-up, unless the subject has confirmation of one or more deterioration criteria (section 3.3.3), in which case a cycloplegic refraction must be performed if not done within the previous 6 months. A mandatory cycloplegic refraction must also be completed at the 30-month and 36-month exams. In addition, a cycloplegic refraction should be performed whenever the investigator suspects that refractive error may not be corrected according to study guidelines (*see below*).

If cycloplegic refraction reveals a change in refractive error of  $\geq 0.75$  D sphere or  $\geq 0.75$  D cylinder or  $\geq 0.75$  D in SE anisometropia or axis change of 6 degrees or more when cylinder is 1.00D or more from the previous cycloplegic refraction, the glasses must be updated. Whether to update the correction for smaller changes in refraction is at investigator discretion. If updated, the glasses correction must meet the requirements described in *sections 3.1.2 and 3.4*.

If the glasses correction drops to +1.00D SE or lower, the use of glasses is at the investigator's discretion.

#### 4.3.1 Bifocals

Bifocal treatment is allowed only following confirmation of deterioration criteria (section 3.3.3). Subjects will be tested in their distance correction placed in a trial frame at the 36-month outcome exam.

### 4.4 Management of Strabismus

Strabismus surgery is not allowed prior to the 36-month outcome exam unless one or more deterioration criteria are confirmed. Subjects who undergo strabismus surgery will return for

1103 follow-up at the protocol-specific follow-up visits. Subjects who receive strabismus surgery prior  
1104 to the 36-month outcome exam will be considered a failure for analysis purposes (see *section 5.2.1*).  
1105

#### 1106 **4.5 Management of Amblyopia**

1107 Amblyopia treatment is not allowed prior to the 36-month outcome exam unless one or more  
1108 deterioration criteria are confirmed. For subjects for whom amblyopia treatment is permitted,  
1109 treatment is at investigator discretion, but must start with prescribing refractive correction  
1110 (described in *section 3.4*). Method used for amblyopia treatment is at investigator discretion. If  
1111 atropine is being used, it must be discontinued at least 2 weeks before the 36-month visit.  
1112

1113 Subjects receiving amblyopia treatment prior to the 36-month outcome exam will be considered a  
1114 deterioration for analysis (regardless of whether a formal deterioration criterion had first been met)  
1115 but will not be considered a failure for analysis purposes unless the amblyopia is present at the time  
1116 of the 36-month outcome exam.  
1117

#### 1118 **4.6 Risks**

1119 There are no risks involved in this study that would not be part of usual care.  
1120

##### 1121 **4.6.1 Risks of Examination Procedures**

1122 The procedures in this study are part of daily eye care practice in the United States and pose no  
1123 known risks. As part of a routine usual-care exam, the participant will receive cycloplegic/dilating  
1124 eye drops.  
1125

#### 1126 **4.7 Reporting of Adverse Events**

1127 No surgical procedures are part of the protocol and no treatments are being prescribed that are not  
1128 part of usual care. Investigators will abide by local IRB reporting requirements.  
1129

#### 1130 **4.8 Discontinuation of Study**

1131 The study may be discontinued by the Steering Committee (with approval of the Data and Safety  
1132 Monitoring Committee) prior to the preplanned completion of enrollment and follow-up for all  
1133 participants.  
1134

#### 1135 **4.9 Travel Reimbursement**

1136 Parents of each participant will be compensated \$40 (by check or by merchandise or money-card)  
1137 per visit for completion of each protocol-specified follow-up visit. If there are extenuating  
1138 circumstances, and the participant is unable to complete study visits without additional funds due to  
1139 travel costs, additional funds may be provided.  
1140

#### 1141 **4.10 Study Costs**

1142 The participant or his/her insurance will be responsible for the costs that are considered standard  
1143 care.  
1144

1145 Standard care visits (paid for by participant or his/her insurance) include:

- 1146 • Initial examination
- 1147 • 12-month follow-up visit

- 1148 • 24-month follow-up visit
- 1149 • 36-month follow-up visit

1150

1151 Non-standard of care visits (paid for by the study) include:

- 1152 • 6-month follow-up visit
- 1153 • 18-month follow-up visit
- 1154 • 30-month follow-up visit
- 1155 • Return for masked exam within 2 weeks after the 6, 12, 18, 24, or 30 month visits or within
- 1156 4 weeks of 36-month exam

1157

1158 All glasses and any changes to glasses that are mandated by the study protocol during the course of  
1159 the study and are required for further testing will be paid for by the study. A change in glasses  
1160 prescribed at the 36-month exam when the subject will not be seen back for study purposes will not  
1161 be paid for by the study. Additional treatment offered at the investigator's discretion during the  
1162 study will not be paid for by the study.

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1165

## CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

### 5.1 Definitions of Primary Cohorts

All analyses will be performed separately for each of the two primary cohorts:

- Subjects aged 12 to <36 months
- Subjects aged 36 to <72 months

### 5.2 Primary Data Analysis

The primary analysis will be a treatment group comparison of the proportion with confirmation of one or more failure criteria (below) at 36 months post-randomization.

The null hypothesis of no difference between the treatment groups will be rejected if the proportion with confirmation of one or more failure criteria in immediate glasses is significantly (higher or) lower than the proportion in observation, based on the 2-sided Fisher's exact test with probability of Type I error of 5%.

The primary analysis will follow the intent-to-treat principle. The primary analysis will not include those patients not completing the 36-month visit. Secondary analyses will be conducted using the last-observation-carried-forward and using multiple imputation with logistic regression for failure status for subjects who fail to complete the 36-month outcome visit. If these secondary results yield similar results to the primary analysis, they will be used to provide supportive evidence for the primary analysis conclusion. If results differ, exploratory analyses will be conducted to evaluate the reasons for the difference.

#### 5.2.1 Classification of Primary Outcome (Failure Criteria)

At the 36-month visit, each subject's condition will be classified as either failure or not a failure as follows:

Failure = ANY of the following criteria are met at the masked 36-month visit both with and without trial frames (without prism or bifocal):

1. Any measurable heterotropia in primary gaze in the distance (3 meters) or at near (1/3 meter) not correctable with distance refractive correction alone
2. Strabismus surgery prior to the 36-month outcome exam
3. Visual acuity below age norms (see Table 1) in either eye
4.  $\geq 2$  logMAR lines of IOD if visual acuity is 20/25 or worse in the better eye (applies to IOD either with or without correction but not one eye with and one eye without)
5.  $\geq 3$  logMAR lines of IOD if visual acuity is 20/20 or better in the better eye (applies to IOD either with or without correction, but not one eye with and one eye without)
6. Stereoacuity at near by Randot Preschool test below age normal values (see Table 2) :

Not Failure = NONE of the criteria for failure are met



If a subject meets any failure criteria (with the exception of strabismus surgery prior to the 36-month outcome exam), the visual condition that is considered to be failed must be retested by the masked examiner (*section 3.6.1*) using the same procedures outlined in *section 3.6.1*. The subject must be given a 10-minute break prior to retesting each failed criterion. Failure criterion must be confirmed with and without correction to be considered a failure.

If failure is confirmed and the subject requires a change in glasses (*section 4.3*), the 36-month outcome exam is repeated on a different day 4 weeks  $\pm$  1 week later by the masked examiner, with the child wearing their new glasses. Testing without correction does NOT need to be repeated. Failure will be assessed at this post-36 month exam, and the subject will be classified as a failure if he/she meets any of the failure criteria above. If the subject meets any failure criteria wearing their new glasses, the visual condition that is considered to be failed must be retested by the masked examiner using the same procedures outlined above. Failure must be confirmed without trial frames at the 36-month exam and with correction at this repeat outcome exam 4-weeks later to be considered a failure.

### **5.3 Secondary Data Analyses**

All secondary analyses will be performed separately for each of the two primary cohorts (*section 5.1*).

#### **5.3.1 Best Visual Acuity at 36 Months**

A treatment group comparison of the mean maximum visual acuity per subject at the masked 36-month visit (best visual acuity on any test with and without correction) will be performed using a t-test.

#### **5.3.2 Development of Strabismus**

A treatment group comparison of the proportion of subjects who develop a measurable heterotropia not correctable with glasses alone at the 36 month masked outcome will be performed using the Fisher's exact test. The cumulative proportion of subjects who develop a measureable heterotropia at any time during follow-up will be compared between treatment groups using the log-rank test.

#### **5.3.3 Subgroup Analysis**

Treatment effect in subgroups based on baseline factors will be assessed. The subgroups of interest include baseline spherical equivalent anisometropia and baseline spherical equivalent refractive error. Outcome failure status at 36 months post-randomization will be tabulated by subgroup and reviewed for consistency. The subgroup definitions for the planned subgroup analyses are as follows:

- Spherical equivalent anisometropia:  $\leq +1.00D$ ,  $> +1.00D$
- Spherical equivalent refractive error:  $+3.00D$  to  $< +4.00D$ ,  $+4.00D$  to  $< +5.00D$ ,  $+5.00D$  to  $+6.00D$
- Masking: unmasked sites, masked sites (including those subjects where masking was not completed)

#### **5.3.4 Observation Group Deterioration**

Proportion of subjects in the observation group who deteriorated during the course of the study will be evaluated and a 95% confidence interval for the proportion will be calculated.

### 5.3.5 Development of Amblyopia

A treatment group comparison of the proportion of subjects who develop amblyopia during the course of the study will be performed using the Fisher's exact test.

### 5.3.6 Near Visual Acuity

A treatment group comparison of the mean near visual acuity at the masked 36-month outcome exam will be performed using a t-test.

## 5.4 Exploratory Analyses

Exploratory analysis will be described fully in the formal analysis plan.

## 5.5 Sample Size Estimates

Sample size has been estimated separately for each of the two primary cohorts. The study is powered for an appropriate number of patients in each primary cohort.

Table 5 provides sample size estimates per treatment group to detect specific differences in the proportion of patients meeting failure criteria at 36 months (section 5.2.1) with 90% power and a two-sided type I error rate of 5% using a Fisher's exact test.

**Table 5: Sample Size Estimates Per Group for Various Failure Proportions**

Failure Proportion: Observation	Failure Proportion: Glasses			
	0.05	0.10	0.15	0.20
0.15	198	951	-	-
0.20	107	282	1248	-
0.25	71	143	352	1502
0.30	51	90	173	411
0.35	40	63	105	197
0.40	32	47	72	118

### Subjects aged 12 to <36 months

Based upon estimates in the literature, the proportion of infants developing a heterotropia or amblyopia after glasses ranged from 6% to 29%.<sup>4, 12, 13</sup> The proportion of infants developing a heterotropia or amblyopia after no glasses ranged from 21 to 68%.<sup>4, 12, 13</sup> Unfortunately, there was a lack of standardization of outcomes in these prior studies. Since failure criteria will be more stringent in this study, and since children will be followed more closely in the current study, we estimate that the failure proportions in the current study will be toward the lower end of these estimates from the literature.

Following discussion with clinicians, the anticipated failure proportion is 10% in the glasses group and 25% in the observation group. Given these failure proportions, a sample size of 143 per treatment group would provide 90% power to detect a difference between the treatment groups, using a 2-sided probability of Type I error of 5%. Adjusting for 10% loss to follow up, and a 5% adjustment for interim monitoring, the study would need to enroll approximately 336 subjects 12 to <36 months old.

### Subjects aged 36 to <72 months

There is essentially no literature to base sample size estimates for 36 to <72 month olds. A sample size of 336 subjects 36 to <72 months old was chosen, the same as that for the younger cohort.

We could speculate that outcome proportions in both treatment groups might be less frequent in the older cohort since children in the younger cohort may have amblyopia or reduced stereoacuity at randomization that is undetected due to inability to test in this age group, or children in the older cohort may have an inherently lower risk of amblyopia, heterotropia, and reduced stereoacuity. Assuming the same anticipated failure proportions as the younger cohort (10% in the glasses group and 25% in the observation group), with the sample size of 143 subjects completing outcome in each treatment group (the same as the younger cohort) the study would have over 90% power to detect a difference between the treatment groups (the study would have 97% power to detect a difference if the true proportions were 5% in the glasses group and 20% in the observation group).

As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 700.

#### **Subjects from Unmasked Sites**

The study will allow up to 20% of subjects in each primary cohort (67 subjects) to be enrolled at unmasked sites.

### **5.6 Interim Analysis**

This study will include a separate interim monitoring plan for each primary cohort that incorporates at least one and up to three interim analyses, consisting of a treatment group comparison of proportion meeting failure criteria at 36 months post-randomization. The monitoring plan will consist of a two-sided boundary for efficacy.<sup>17</sup> This will allow for early stopping to be considered in the event that interim data strongly support a treatment effect favoring glasses. The interim monitoring is unlikely to affect study recruitment since recruitment is likely to end before the 36-month outcome is reached; only study follow-up of enrolled subjects will be affected.

The DSMC will monitor the cumulative proportion of subjects that deteriorate within treatment group, by masking status. If the cumulative proportion that deteriorates appears to differ by masking status within treatment group, recruitment may be stopped in unmasked sites.

A formal statistical plan for interim monitoring of primary outcome data will be developed in conjunction with the DSMC and incorporated into the statistical analysis plan prior to any analysis of primary or secondary outcome data.

## CHAPTER 6: REFERENCES

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