# AMBLYOPIA TREATMENT STUDY

# An Observational Study of Optical Correction for Strabismic Amblyopia in Children 3 to <7 Years Old

## PROTOCOL

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# CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG). It is one of a series of randomized trials and observational studies that address management issues related to the treatment of amblyopia in children.

## 1.1 Background Information

This study will evaluate the effectiveness of refractive correction alone for the treatment of previously untreated strabismic or combined-mechanism amblyopia in children 3 to <7 years old with visual acuity of 20/40 to 20/400.

A recently completed PEDIG study (ATS5) found that in 3 to <7-year-old children with previously untreated anisometropic amblyopia, refractive correction alone improved visual acuity by 2 or more lines in 77% of the patients and amblyopia resolved in at least one third of the patients.[1] These results supported previous observations from retrospective and pilot studies[2-5] as well as Stewart et al's prospective report[6] on 18 children with anisometropic amblyopia whose visual acuity improved after treatment with spectacle correction only.

Improvement in amblyopic eye visual acuity from treatment with optimum refractive correction in cases of anisometropic amblyopia is plausible because the refractive correction treats the underlying amblyogenic condition (i.e., uncorrected unequal refractive error) by providing retinal images of more similar clarity, size, and contrast. Elimination of the dissimilar retinal images, which may act as barriers to normal visual input, allows the amblyopic eye to receive appropriate visual stimulation. In contrast, visual acuity improvement with refractive correction alone in cases of amblyopia associated with strabismus is not expected to occur when the refractive correction does not completely eliminate the strabismus and restore fusion. In such cases, the underlying amblyogenic factor of a manifest ocular deviation remains; consequently, active cortical inhibition is presumably still present. Nonetheless, Stewart and colleagues recently reported finding gains in amblyopic eye visual acuity of children with strabismic and combined-mechanism amblyopia after a period of treatment with refractive correction alone.[6] The PEDIG also observed this to occur in a subgroup of children with previously untreated strabismic and combined-mechanism amblyopia in a recent study.[7] Amblyopic eye acuity improved by ≥ 2 lines from spectacle-corrected baseline acuity in 9 (75%; 95% CI = 43% - 95%) of the 12 patients with strabismic amblyopia and in 9 (69%, 95% CI = 39% - 91%) of the 13 patients with combined-mechanism amblyopia. Mean change from baseline to maximum improvement was 2.2 $\pm$ 1.8 and 2.6 $\pm$ 2.0 lines, respectively. These results are similar to those of Stewart and colleagues[6] who reported visual acuity improvement averaging 3.0 lines in 16 children with strabismic amblyopia and 1.9 lines in 31 children with combined-mechanism amblyopia.

Although our results support the suggestion of Stewart et al.[6] that strabismic amblyopia can improve with spectacle correction alone, they are not conclusive because both studies had small numbers of patients. Also, our classification of strabismus was based on alignment without refractive correction. Thus, a larger controlled study is needed to confirm or refute these findings in patients with strabismic and combined-mechanism amblyopia.

The ideal study design to answer the question of whether spectacles alone can significantly improve amblyopic eye visual acuity in strabismic children is a randomized trial with a control group who does not receive optical correction. However, most pediatric eye care providers would be reluctant to randomize esotropic children with hyperopic refractive error to a control

group of no optical correction because of the likelihood of some children having accommodative esotropia, which would necessitate that hyperopic spectacles be prescribed. The number of esotropic amblyopes without an accommodative component is sufficiently few to make a randomized trial not feasible. Therefore, we have chosen to perform an observational study with a large number of children with pure strabismic and combined-mechanism amblyopia in order to evaluate the effect of refractive correction in this population of patients.

### 1.2 Study Objective

To evaluate the effectiveness of refractive correction alone for the treatment of previously untreated strabismic or combined-mechanism amblyopia in children 3 to <7 years old.

### 1.3 Synopsis of Study Design

Major Eligibility Criteria *(see section 2.2 for a complete listing)*

- Age 3 to < 7 years
- Amblyopia associated with strabismus (with or without anisometropia)
- Visual acuity in the amblyopic eye between 20/40 and 20/400 inclusive through best refractive correction
- Visual acuity in the sound eye 20/40 or better and inter-eye acuity difference ≥3 logMAR lines through best refractive correction
- Refractive error meeting at least 1 of the following criteria: ≥ 1.00D of astigmatism in the amblyopic eye, ≥ 1.00D spherical equivalent anisometropia, or ≥ +2.00D spherical equivalent hyperopia in either eye
- No prior amblyopia therapy
- No previous spectacle wear
- Investigator wishes to prescribe spectacles for refractive correction

Treatment

Patients will receive spectacles to correct their refractive error.

Visit Schedule

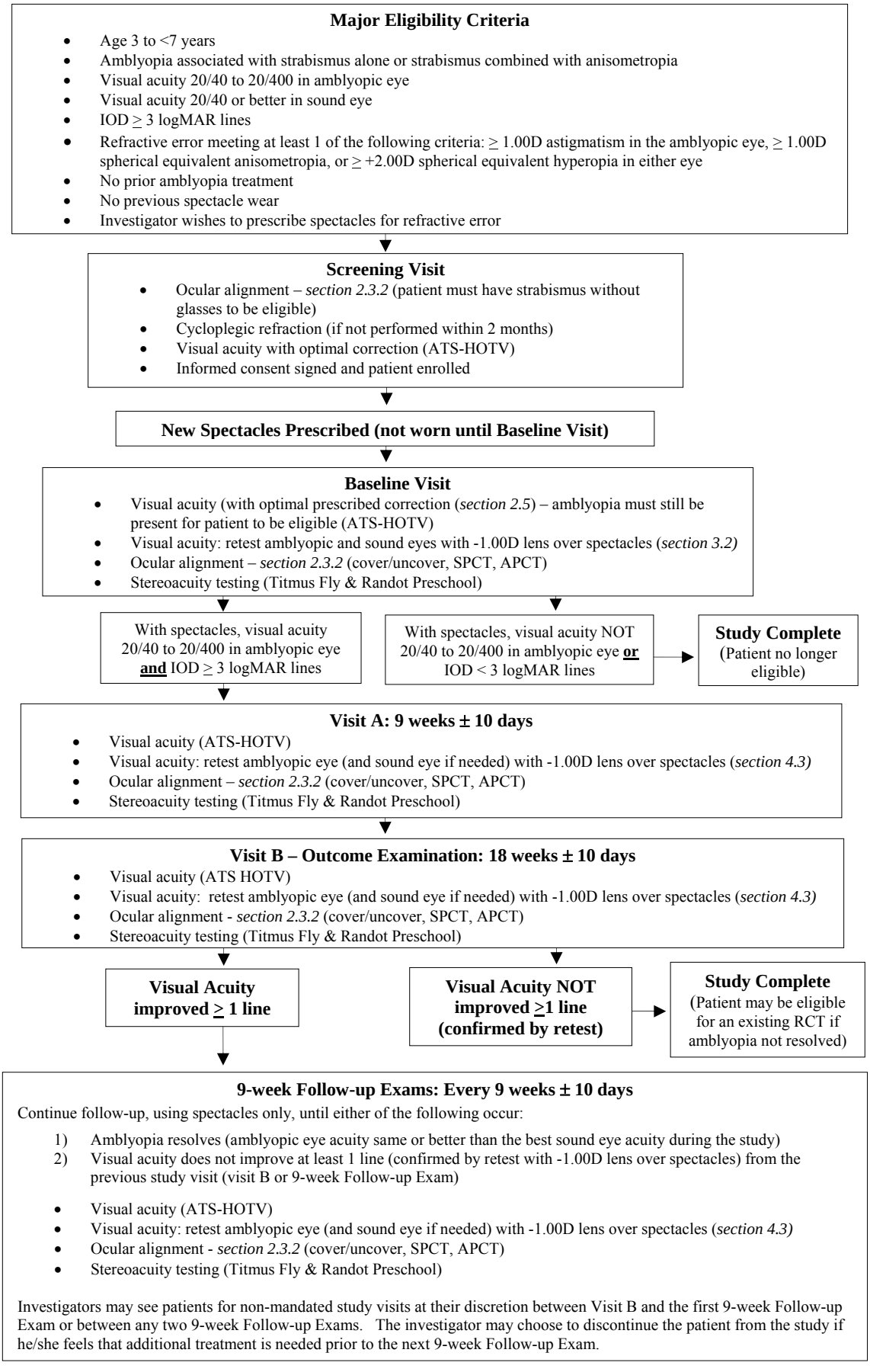
- Baseline exam
- Visit A: 9 weeks ±10 days
- Visit B: 18 weeks ±10 days (outcome exam by ATS certified examiner)
- 9-week Follow-up Exams: every 9 weeks ± 10 days (if needed- *section 4.5*) until amblyopia resolves or until visual acuity does not improve at least 1 line (confirmed by a retest using a -1.00D lens over spectacles) from the previous study visit (*section 4.5*).

At each visit, distance visual acuity will be assessed in each eye, and ocular alignment and stereoacuity testing will be performed.

Primary Analysis

As defined in the analysis plan, separate analyses will be conducted for three patient subgroups based on the proposed mechanisms of visual acuity improvement. The proportion of patients in these groups with 2 or more lines improvement in amblyopic eye visual acuity will be calculated and exact 95% confidence intervals will be computed. Point estimates and 95% confidence intervals for the mean lines of improvement in amblyopic eye visual acuity from baseline to the 18-week outcome exam will also be calculated. For each patient, the maximum acuity (at 18 weeks or after) and the visit at which this occurred will be determined. Analysis of visual acuity at this last visit will parallel the analysis done on visual acuity at 18 weeks.

## 1.4 Study Summary Flow Chart



# CHAPTER 2: SCREENING & PATIENT ENROLLMENT

## 2.1 Eligibility Assessment and Informed Consent

A patient is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard care) that identifies amblyopia meeting the eligibility criteria.

For patients who appear eligible for the study following a "standard-care" or preliminary examination, 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

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

1. Age 3-<7 years
2. Able to perform visual acuity testing using the ATS single-surround HOTV protocol
3. Amblyopia associated with strabismus (comitant or incomitant) with or without anisometropia
   - At least one of the following criteria must be met:
     - Heterotropia at distance and/or near fixation on examination (without spectacles)
     - History of strabismus surgery (or botulinum toxin extraocular muscle injection)
     - Documented history of strabismus that is no longer present (and which in the judgment of the investigator is the cause of amblyopia)
4. Visual acuity measured in each eye according to the procedures described in *section 2.3.2* that meet the following criteria:
   - Amblyopic eye 20/40 to 20/400 inclusive
   - Sound eye $\geq$20/40
   - Inter-eye acuity difference $\geq$3 logMAR lines (i.e., amblyopic eye acuity at least 3 logMAR lines worse than sound eye acuity)
5. No previous spectacle correction
6. Refractive error meeting at least 1 of the following criteria: $\geq$ 1.00D of astigmatism in the amblyopic eye, $\geq$ 1.00D spherical equivalent anisometropia, or $\geq$ +2.00D spherical equivalent hyperopia in either eye.
7. Investigator wishes to prescribe spectacles to correct refractive error
8. No prior amblyopia treatment
9. No current vision therapy or orthoptics
10. No ocular cause for reduced visual acuity
    - Nystagmus per se does not exclude the patient if the above visual acuity criteria are met
11. Ocular examination within 2 months prior to enrollment
12. Cycloplegic refraction within 2 months prior to enrollment
13. No myopia ($\geq$ -0.25D spherical equivalent)
14. No prior intraocular or refractive surgery
15. No strabismus surgery planned in the 9 weeks following the Baseline Visit
16. Parent understands protocol and is willing to accept treatment
17. Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff
18. Relocation outside of area of an active ATS site within next 6 months not anticipated

## 2.3 Screening Examination Procedures

### 2.3.1 Historical Information

Historical information elicited will include the following: date of birth, gender, race, ethnicity, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, filters), and spectacle correction.

### 2.3.2 Testing Procedures

1. Ocular Alignment Testing: Ocular alignment at distance and near will be assessed with the cover/uncover test to determine if a tropia is present; if present, it must be determined whether the frequency is constant or intermittent.
    - Strabismic deviations will be measured first with the Simultaneous Prism and Cover Test (SPCT) and then by the Alternate Prism and Cover Test (APCT) in primary position at distance and near using the methods as outlined in the ATS Testing Procedures Manual. The SPCT measurements should always be performed before the APCT measurements.
    - Testing must be performed prior to cycloplegia.
    - Measurements made using the Krimsky test are NOT allowed.
    - Testing must be performed no more than 7 days prior to enrollment.

2. Visual Acuity Testing: Visual acuity testing will be done by a certified examiner using the ATS single-surround HOTV letter protocol on the Electronic Visual Acuity Tester. The protocol for conducting visual acuity testing is described in the ATS Testing Procedures Manual. Aspects of the testing protocol that are specific to this study are:
    1. Testing is performed with the optimal refractive correction (*section 2.5*) as determined from a cycloplegic refraction completed no more than 2 months prior.
    2. Testing can be performed without cycloplegia or after cycloplegia when the child is sufficiently attentive for this to be accomplished (*although it is preferable that testing be done without cycloplegia*).
    3. Testing must be performed no more than 7 days prior to enrollment.

    If the patient is uncooperative because of resistance to wearing trial frames or using a phoropter, he/she should be given a 15-minute break before attempting to retest. If the patient is still uncooperative and visual acuity is not attainable, the child can not be enrolled in the study at this time. However, the patient may be retested on a different day provided no spectacles are worn in the interim.

3. Additional Clinical Testing:
    1. Ocular examination as per investigator's clinical routine to rule out a cause for reduced visual acuity other than amblyopia
        - If performed within prior 2 months, do not need to repeat at time of enrollment
    2. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
        - If performed within prior 2 months, do not need to repeat at time of enrollment

## 2.4 Enrollment of Consented Patients

Once the parent(s) of the patient meeting the overall eligibility criteria have given consent to enter the study, the patient will be enrolled in the study using the website study enrollment process.

## 2.5 Spectacle Correction

The following guidelines apply for prescribing spectacles for all patients who choose to enroll in the study:

- Full correction of anisometropia
- Full correction of astigmatism
- Hyperopia either fully corrected or symmetrically undercorrected by **no more than +0.50D**
- Bifocals should not be prescribed prior to the Baseline Visit; however, they may be prescribed at any subsequent visit if the esotropia at near exceeds the esotropia at distance after wearing the single vision glasses.

## 2.6 Obtaining Spectacles

Patients who choose to enroll in the study will be sent to a study-certified optician to have the spectacles made.

The spectacles will either be sent directly to the investigator or picked up by the patient on the day of or day prior to the Baseline Visit. The new spectacles should be carried to the office between pickup and the Baseline Visit. The new spectacles should not be worn prior to the Baseline Visit.

All enrolled patients will have a Baseline Visit within 30 days of the Screening Visit. The visit needs to be scheduled such that the spectacles prescribed at the Screening Visit will be available, as trial frames are not allowed to be used for visual acuity testing at the Baseline Visit.

Prior to the Baseline Visit, the office staff should verify that the spectacles prescribed at the Screening Visit have been received or that the patient will be picking them up on the day of the Baseline Visit.

# CHAPTER 3: BASELINE VISIT

## 3.1 Baseline Visit

All enrolled patients will have a Baseline Visit within 30 days after the Screening Visit. At this Baseline Visit, the new spectacles with the optimal refractive correction based on the cycloplegic refraction will be placed on the child for the first time.

## 3.2 Procedures at the Baseline Visit

1. The spectacles prescription should be verified with a lensometer.
    - Sphere and cylinder power must be within 0.25 D of the prescribed correction. Cylinder axis must be within 6 degrees of the axis in the spectacles when cylinder power is >1.00D. If these criteria are not met, the spectacles must be re-made and the patient will return at a later date for the Baseline Visit.
2. The patient should wear the new spectacles for 10 to 30 minutes before the testing in #3-5 below is performed.
3. Visual acuity testing will be done without cycloplegia by a certified examiner using the ATS single-surround HOTV letter protocol on the Electronic Visual Acuity Tester. Both the amblyopic and sound eyes must be retested on the same day with a -1.00D lens over the new spectacles (thus decreasing the chance that any persistent accommodative tone will compromise distance visual acuity and making it more likely that best-corrected visual acuity is measured). Baseline visual acuity is considered the better of the two acuity measures. The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual.
4. Ocular alignment with the cover/uncover test, SPCT, and APCT (*section 2.3.2*) at distance and near is evaluated through the new spectacles.
5. Stereoacuity with the Titmus fly and Randot Preschool Stereoacuity tests

## 3.3 Visual Acuity Change

### 3.3.1 Presumed Latent Hyperopia

If visual acuity improves when the child is tested with a -1.00D lens over the spectacles compared to the initial visual acuity measured at the Baseline Visit without the minus lens, the investigator should consider the possibility of persistent accommodative tone and either change the spectacles (if changed, the hypermetropic correction can only be symmetrically undercorrected by no more than 0.50 D from the cycloplegic refraction – *section 2.5*) or wait and allow the patient to relax into them.

- If spectacles are changed (*section 3.3.3*), the patient must return for the Baseline Visit at a later date.
- Investigators may choose not to change spectacles at the Baseline Visit because of the expectation that the patient will relax his/her accommodation over time. However, if the investigator feels that the patient will require assistance relaxing his/her accommodation, the investigator must call the Protocol Chair to discuss management options, which may include bilateral cycloplegia. If the spectacles are not changed, patients will not be required to return for another Baseline Visit; relaxation of accommodative tone will be verified at Visit A (9-week Visit). The visual acuity recorded at the Baseline Visit will be the better of the two acuities (with or without the -1.00D lens over spectacles). If visual acuity at Visit A (9-week Visit) has not improved to be the same or better than the visual acuity obtained using the minus lens at

the Baseline Visit, the spectacles should be changed at Visit A according to *section 2.5* if a refraction and visual acuity testing confirm a better visual acuity with a change in refraction.

If at the Baseline Visit, the minus lens does not improve visual acuity compared to the initial visual acuity measured at the Baseline Visit without the minus lens, the patient can begin the study unless the investigator suspects an error in refraction, in which case a cycloplegic refraction should be performed. If the original refraction was not correct, the spectacles should be changed (*section 3.3.3*), and the patient should return for the Baseline Visit at a later date.

### 3.3.2 Other Cases of Reduced Visual Acuity

If at the Baseline Visit, visual acuity with spectacles in either eye is worse than the visual acuity at the Screening Visit with trial frames, the investigator should suspect an error in refraction, and consider a cycloplegic refraction (though not mandated). If performed and the original refraction is not correct, the spectacles should be changed (*section 3.3.3*), and the patient should return for the Baseline Visit at a later date.

### 3.3.3 Changing Spectacles

When spectacles with optimal correction are not available at the Baseline Visit, whether due to the spectacles having been made incorrectly or because a new correction needs to be prescribed, the spectacles should be changed according to the criteria listed in *section 2.5*. The patient should not wear the original spectacles prescribed when enrolled into the study until he or she returns at a later date for the Baseline Visit with the new spectacles. If a spectacle change is required at the Baseline Visit, bifocals should not be prescribed at this time; however, they may be prescribed at any subsequent visit if the esotropia at near exceeds the esotropia at distance after wearing the single vision glasses.

## 3.4 Assessment of Eligibility at Baseline

The patient must have strabismus or a history of strabismus associated with amblyopia (*section 2.2*) at the time of enrollment. Regardless of whether the strabismus remains after wearing the optimal spectacles for 10-30 minutes, the patient will remain in the study provided the patient still meets the eligibility criteria for amblyopia (visual acuity criteria for amblyopic and sound eyes and interocular difference – *section 2.2*) while wearing the spectacles. If the patient has better than 20/40 visual acuity in the amblyopic eye, worse than 20/40 visual acuity in the sound eye, or < 0.3 logMAR interocular difference, the patient is no longer eligible for the study.

# CHAPTER 4: TREATMENT AND FOLLOW UP

## 4.1 Treatment

Each patient will receive spectacles with his/her optimal correction (*section 2.5*), paid for by the study. No additional treatment will be provided to patients in this study.

- If a patient receives active treatment (e.g., patching, atropine, filters, visual therapy) of any kind, the patient will end study follow-up.
- If glasses are worn prior to the baseline visit for more than one day, the patient will end study follow-up.

## 4.2 Visit Schedule

- Visit A: 9 weeks ±10 days
- Visit B (Outcome examination by ATS certified examiner): 18 weeks ±10 days
- 9-week Follow-up Exams (if required- *section 4.5*): every 9 weeks ± 10 days until amblyopia resolves (amblyopic eye acuity better than or equal to the best sound eye acuity) or until visual acuity in the amblyopic eye does not improve at least 1 line (confirmed by a retest with a -1.00D lens over spectacles) from the previous study visit (either visit B or prior 9-week Follow-up Exam).

## 4.3 Testing Procedures

1. Visual acuity testing at all follow-up exams will be done without cycloplegia by a certified examiner using the ATS single-surround HOTV letter protocol on the Electronic Visual Acuity Tester.
   - Amblyopic eye visual acuity must also be retested with a -1.00D lens over the optimal refraction (to account for possible persistent accommodative tone).
   - If the sound eye visual acuity is reduced 1 or more lines from the previous visit, the sound eye must also be retested with a -1.00D lens over the optimal spectacle correction.
   - Follow-up visual acuity is considered the better of the two acuity measures (with and without the -1.00D lens). The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual.
   - For Visit B (18-week outcome exam) and all subsequent exams, if the better of the two visual acuities (with and without the -1.00D lens over spectacles) is not at least 1 line better than the visual acuity from the previous study visit, the study ends for this patient. If the better of the two visual acuities (with and without the -1.00D lens) is at least 1 line better than the visual acuity at the previous study visit, study follow-up continues.
2. Detection of strabismus at distance and near by cover/uncover testing, with measurement of any strabismus using the Simultaneous Prism and Cover Test (SPCT) and the Alternate Prism and Cover Test (APCT) (*section 2.3.2*) is performed through the optimal refractive correction. The SPCT should be performed before the APCT (*section 2.3.2*).
   - If the spectacles are bifocals, ocular alignment at near should be tested through the bifocal portion of the lenses. If necessary, the bifocals should be raised to ensure that the patient is viewing the near target in primary position (not down gaze) while looking through the bifocal lenses.
3. Stereoacuity with the Titmus Fly and Randot Preschool Stereoacuity tests

### 4.4 Changes in Treatment Prior to the 18-week Outcome Visit

- Amblyopia treatment in addition to spectacles (e.g., patching, atropine, vision therapy, filters) is NOT allowed prior to the 18-week outcome exam.
- If the investigator determines that a spectacle change is required after the child has worn the glasses initially prescribed, spectacles may be changed prior to the 18-week outcome exam. Bifocals may be prescribed at any visit after the Baseline Visit if the esotropia at near exceeds the esotropia at distance after wearing the single vision glasses.

### 4.5 Follow-up Exams for Patients Still Improving

Beginning at Visit B (18-week outcome exam) and for subsequent study visits, visual acuity in the amblyopic eye will be classified as "stable" or "improving" based on the following criteria:

- Vision is considered "stable" when amblyopic eye visual acuity has not improved at least 1 line (confirmed by a retest with a -1.00D lens over spectacles) from the previous study visit (Visit B or subsequent 9-week Follow-up Exam).
- Vision is "improving" when amblyopic eye visual acuity has improved 1 or more lines from the previous study visit.

- ➢ If vision at Visit B (18-week outcome examination) or a subsequent 9-week Follow-up Exam is classified as "stable," the study is complete for this patient.
- ➢ If vision is classified as "improving," additional 9-week Follow-up Exams will be scheduled every 9-weeks (± 10 days) until vision is classified as "stable."

Testing at each 9-week Follow-up Exam will include the procedures listed in *section 4.3*. (visual acuity, ocular alignment, and stereoacuity).

### 4.6 Non-study Visits

Non-study Visits may be scheduled at the discretion of the investigator between Visit B (18-week outcome exam) and the first 9-week Follow-up Exam or between any two subsequent 9-week Follow-up Exams. The investigator may discontinue the patient from the study if he or she feels strongly that treatment in addition to spectacles is required.

Data from Non-study Visits will not be collected. Determination of visual acuity improvement is made based on visual acuity measurements from Visit B (18-week outcome exam) and subsequent 9-week Follow-up Exams.

### 4.7 Treatment Changes Following the 18-week Outcome Visit

- If the investigator determines that a spectacle change is required, spectacles may be changed following the 18-week outcome exam. Bifocals may be prescribed if the esotropia at near exceeds the esotropia at distance after wearing the single vision glasses.
- Although discouraged, additional treatment may be started at any 9-week Follow-up exam or Non-study Visit following the 18-week Outcome Visit if the investigator feels strongly that treatment in addition to spectacles is required, even if the visual acuity has improved 1 line or more from the previous study visit. Starting any additional treatment will discontinue the patient from the study.

# CHAPTER 5: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

## 5.1 Maintaining Patient Follow-up

The Jaeb Center will maintain direct contact with the parents of each patient. 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 family and to help coordinate scheduling of the outcome examination. Additional contacts will be made if necessary for the scheduling of follow-up visits.

## 5.2 Patient Withdrawals

A patient (and in this case the parents) may withdraw 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 should personally attempt to speak with them and determine the reason. If they do not want to change their child's eye care provider, every effort should be made to comply with this and at the same time try to keep the patient in the study under the new provider's care.

## 5.3 Management of Optical Correction

A refraction should be performed whenever the investigator suspects that refractive error may not be optimally corrected. If a spectacle change is needed, including the prescription of bifocal lenses, the cost of the lenses will be paid for by the study.

## 5.4 Management of Strabismus

Strabismus surgery is not allowed in the first 9 weeks of the study. Strabismus surgery is allowed at the investigator's discretion following Visit A (9-week exam), although it is *strongly* preferred that surgery be delayed until after the 18-week outcome exam. Any surgeries performed during the study will be recorded in the comment section of the Follow-up Examination Form.

## 5.5 Risks of Examination Procedures

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

## 5.6 Reporting of Adverse Events

There is no adverse event reporting in this protocol. No procedures are being performed and no treatments are being prescribed that are not part of usual care. Investigators will abide by local IRB reporting requirements.

## 5.7 Discontinuation of Study

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

## 5.8 Patient Payments

The parent of each patient will be compensated $25 per visit for completion of the 9-week and 18-week visits. For patients remaining in follow up after the 18-week visit, $25 will be paid for each 9-week Follow-up Exam, up to an additional $100 (4 exams). The total maximum compensation for the study is $150. If there are extenuating circumstances, additional funds may be provided for

travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

### 5.9 Benefits of Participation

All patients will be given spectacles. Some patients will have an improvement in amblyopic eye acuity and in some patients, amblyopia may resolve, obviating the need for additional treatment.

# CHAPTER 6: 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, which will supersede these sections when it is finalized.

## 6.1 Data Analysis

The study is evaluating 2 mechanisms by which strabismic amblyopia (with and without anisometropia) may be successfully treated by spectacle correction alone:

1. Correcting small amounts of blur (including small amounts of anisometropia), with a resultant focused foveal image, may be beneficial in strabismic and combined-mechanism amblyopia (even if the amblyopic eye is not fixing or when there is no reduction in the angle of deviation).
2. Correcting moderate amounts of hyperopia might reduce the magnitude of the strabismus, which may be beneficial to the amblyopic eye.

Patients will be classified into one of three groups based on the proposed mechanism of improvement:

1. Potentially improved because of the clear image hypothesis (amblyopic eye ≥1.00D astigmatism and/or ≥ 1.00D spherical equivalent anisometropia with no change in angle size at distance and near). A change in angle is defined as a reduction of 10Δ or more.
2. Potentially improved because of a reduced angle of strabismus (reduction of 10Δ or more at either distance or near)
3. Combination of improved image clarity and reduced angle size

Separate analyses will be conducted within these mechanistic subgroups. Patients dropped from the study before the 18-week outcome exam or who have had strabismus surgery before the 18-week outcome exam will not be included in the analysis.

For groups 2 and 3 above, an exploratory analysis will be performed based on change in strabismic angle size during the study. This will be defined as the change in magnitude from baseline to best alignment in order to categorize patients as:

- Change from heterotropia of >10Δ to a microtropia (≤10Δ) or orthotropia at either distance or near
- Reduction of 10Δ or more at either distance or near
- Reduction of less than 10Δ or an increase in magnitude of deviation

### 6.1.1 Visual Acuity

Within each mechanistic subgroup, the proportion of patients with a 2 or more line improvement in amblyopic eye visual acuity will be calculated and an exact 95% confidence interval will be computed. A point estimate and 95% confidence interval for the mean lines of improvement in amblyopic eye visual acuity from baseline to 18 weeks will also be calculated. For each patient, the maximum acuity (at 18 weeks or after) and the visit at which this occurred will be determined. Analysis of acuity at this last visit will parallel the analysis done on visual acuity at 18-week outcome examination.

In the ATS5 spectacle phase,[7] the 23 patients with amblyopia cause defined as strabismus alone improved an average of 2.0 lines (SD = 1.5), with 74% improving 2 or more lines. The 42 patients with cause defined as combined-mechanism improved an average of 2.5 lines (SD = 2.0), with 64% improving 2 or more lines.

### 6.1.2 Factors Associated with Improvement in Visual Acuity

Exploratory analysis will evaluate whether patient factors such as magnitude of refractive error, baseline visual acuity, magnitude of anisometropia, stereoacuity, and change in magnitude of ocular deviation are associated with visual acuity improvement in the amblyopic eye.

### 6.1.3 Stereopsis and Ocular Alignment

To evaluate whether spectacle correction alone improves stereopsis and ocular alignment in patients not having surgery for strabismus, frequency distributions and cross-tabulations will be performed for the following:

- Stereoacuity as measured by the Randot Preschool Stereoacuity Test at the time of best amblyopic eye visual acuity compared with the stereoacuity at baseline with correction.
- Ocular alignment prior to spectacle wear compared with alignment after initial spectacle wear.
- Ocular alignment at the time of best amblyopic eye visual acuity compared with the alignment at baseline.

## 6.2 Sample Size

Up to 150 patients will be enrolled. Recruitment may be discontinued if this goal is not reached within two years.

Based upon recruitment data from ATS5, it is estimated that 2 years of recruitment will result in the enrollment of 150 patients (about 6 per month) with amblyopia caused by strabismus (alone or with anisometropia), all of whom have had no prior treatment (including spectacles) for amblyopia. Assuming 90% of enrolled patients complete the study, we may expect to have 135 patients for analysis.

The tables below estimate the levels of expected precision with sample sizes of varying arbitrarily chosen subgroup proportions:

**Half-width of 95% Confidence Intervals for Mean Amblyopic Eye Improvement**

| | **Subgroup % of patients (N=135 patients overall)** | | |
|---|---|---|---|
| **Amount of Variation in Lines of Improvement (SD)** | **25% N=34** | **50% N=68** | **75% N=102** |
| | *half-width of 95% confidence interval on mean improvement* | | |
| **SD = 1.0 lines** | 0.3 | 0.2 | 0.2 |
| **SD = 1.5 lines** | 0.5 | 0.4 | 0.3 |
| **SD = 2.0 lines** | 0.7 | 0.5 | 0.4 |
| **SD = 2.5 lines** | 0.8 | 0.6 | 0.5 |

**Half-width of 95% Confidence Intervals**
**for Proportion of Patients with 2 or More Lines Improvement in the Amblyopic Eye**

| | **Subgroup % of patients (N=135 patients overall)** | | |
|---|---|---|---|
| **Proportion of Patients with 2 or More Lines Improvement** | **25% N=34** | **50% N=68** | **75% N=102** |
| | *half-width of 95% confidence interval on proportion* | | |
| **.40** | 0.17 | 0.12 | 0.10 |
| **.30** | 0.15 | 0.11 | 0.09 |
| **.20** | 0.13 | 0.10 | 0.08 |
| **.10** | 0.10 | 0.07 | 0.06 |

# CHAPTER 7: REFERENCES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