Bilateral Refractive Amblyopia Treatment Study

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CONTACT INFORMATION

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1. Objectives

1. To determine the amount of visual acuity improvement with treatment of presumed bilateral refractive amblyopia
2. To determine the time course of visual acuity improvement with treatment

1.2. Background

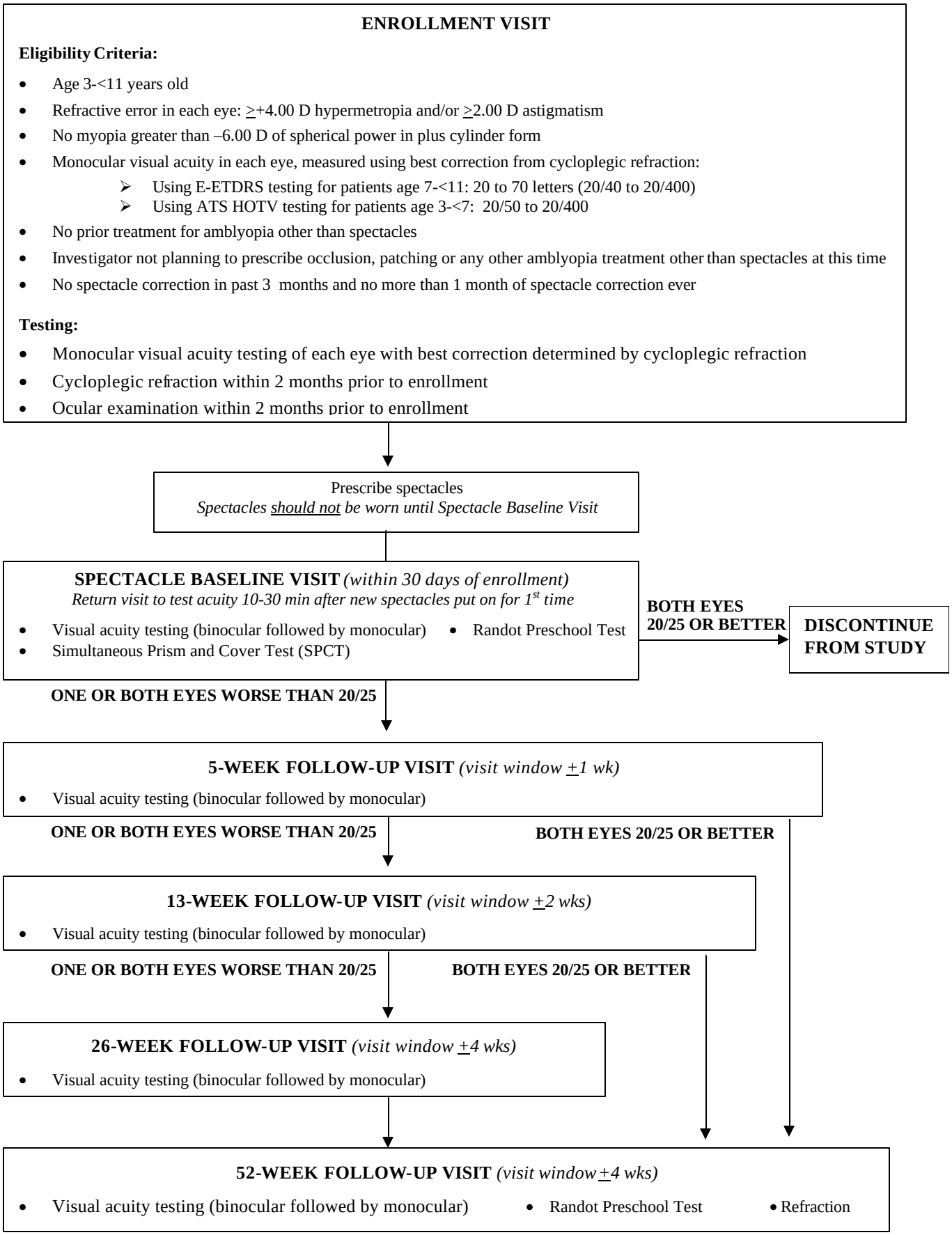
There is a paucity of literature on bilateral amblyopia that is due to a substantial amount of refractive error (hypermetropia or astigmatism), and it is limited principally to review articles and case reports.[1-6] The incidence is not known, but in one study, 4 of 830 (0.5%) children examined at the time of entry into school had bilateral amblyopia.[6] Schoenleber et al[3] performed a retrospective review of office records and identified 184 children with $\geq$ +4.00 diopters of hypermetropia in both eyes, 12 of whom (6.5%) had bilateral amblyopia of 20/50 or worse. Ten of the 12 children (83%) improved to 20/40 or better in both eyes over a mean follow-up time of 22 months. Werner and Scott[4] reported 6 cases of bilateral hypermetropic amblyopia with a spherical equivalent of at least +5.00 D and an initial visual acuity of 20/40 or worse in both eyes. All 5 patients with follow up improved with glasses alone, and 2 of these 5 had a most recent visual acuity worse than 20/40 in one eye with follow-up less than one year. Cavazos et al[2] identified 218 eyes with hyperopia $\geq$ +5.00 D or astigmatism $\geq$+2.00 D. Of these, 82 (38%) of the dominant eyes had an initial corrected visual acuity less than 20/25. Most improved to $\geq$ 20/25, but many patients were lost to follow-up. In ongoing studies, bilateral refractive amblyopia is being evaluated in Native Americans.[7]

The PEDIG network offers an opportunity to collect prospective data on uncommon conditions such as bilateral refractive amblyopia.

1.3. Study Summary

1. Patients will be enrolled who have bilateral refractive error with hyperopia $\geq$+4.00 D and/or astigmatism $\geq$2.00 D and have visual acuity in each eye, measured using best correction derived from cycloplegic refraction, meeting the following criteria:
   - Using E-ETDRS testing for patients age 7-<11 years: visual acuity 20 to 70 letters (20/40 to 20/400)
   - Using ATS HOTV testing for patients age 3-<7 years visual acuity 20/50 to 20/400
2. Enrolled patients will be prescribed spectacles, which will be paid for by the study.
3. The patient will return for a Spectacle Baseline visit within 30 days, at which time the spectacles will be placed on the patient for the first time and binocular and monocular visual acuities will be measured.
   - Patients whose monocular acuity at the Spectacle Baseline Visit is 20/25 or better in both eyes will end the study
   - Patients whose monocular acuity at the Spectacle Baseline Visit is worse than 20/25 in at least one eye will begin a one-year period of study follow up
4. Follow-up visits are required at 5$\pm$1 week, 13$\pm$2 weeks, 26$\pm$4 weeks, and 52$\pm$4 weeks.
   - If at any follow-up visit a patient's monocular acuity is 20/25 or better in both eyes, the patient should return for the 52-week visit only and may skip the interim follow-up visits.

1.4. Study Flowchart



CHAPTER 2: ENROLLMENT VISIT

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 presumed bilateral refractive 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). Parent(s) or guardian(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 or guardian prior to performing any study-specific procedures and collecting any data 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 - <11 years

2. Able to perform single-surrounded single optotype visual acuity using the ATS HOTV protocol for children 3 to <7 years old and using the E-ETDRS protocol for children 7 to <11 years old

3. Monocular visual acuity in each eye, measured using trial frames or phoropter with best correction derived from cycloplegic refraction, meeting the following criteria:
   - Using E-ETDRS testing for patients age 7-<11 years: visual acuity 20 to 70 letters (20/40 to 20/400)
   - Using ATS HOTV testing for patients age 3-<7 years acuity 20/50 to 20/400

4. Refractive error that meets at least one of the following criteria in <u>each</u> eye:
   - Spherical equivalent $\geq$+4.00 D
   - Astigmatism $\geq$2.00 D

5. Investigator believes that the patient's reduced visual acuity is due to bilateral, refractive amblyopia

6. No myopia greater than –6.00 D of spherical power in plus cylinder form

7. No ocular cause for decreased acuity in either eye; nystagmus per se will not exclude a patient from the study

8. No refractive correction (spectacles or contact lenses) in past three months and no more than 1 month of refractive correction ever

9. No prior treatment for amblyopia (other than the refractive correction permitted in #8)

10. Investigator not planning to prescribe occlusion, patching or any other amblyopia treatment other than spectacles at this time

11. Cycloplegic refraction and ocular examination within 2 months prior to enrollment

12. No prior intraocular or refractive surgery

13. No use of contact lenses during the study

14. Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff

15. Relocation outside of an area with an active ATS site within next year not anticipated

2.3. Enrollment Examination Procedures

The following testing will be completed at the visit:

- Cycloplegic refraction
- Visual acuity testing with best correction (see section 2.3.1.)
- Ocular examination

For the cycloplegic refraction and the ocular exam, if the procedure has been performed within the prior 2 months by a study investigator, it does not need to be repeated at time of enrollment. The standard protocol for each procedure is described in the PEDIG Testing Procedures Manual.

Historical information will also be collected and will include the following: date of birth, gender, race, ethnicity, and prior spectacle wear.

2.3.1. Visual Acuity Testing

Visual acuity testing will be measured monocularly in each eye at distance using trial frames or phoropter with best correction. Testing will be performed by a certified examiner using the Electronic Visual Acuity Tester or a study-approved alternative instrument.

The protocol used for visual acuity testing is age-specific:

- Patients aged 3-<7 years will use the ATS HOTV protocol
- Patients aged 7-<11 years will use the E-ETDRS testing protocol

The protocols for conducting the visual acuity testing are described in the PEDIG Testing Procedures Manual.

Aspects of the testing protocol that are specific to this study are indicated below:

1. Testing must be done no more than 7 days prior to enrollment.
2. If a cycloplegic refraction is done at this visit, testing can be done after cycloplegia when the child is sufficiently attentive for this to be accomplished.
3. Testing is done using trial frames or a phoropter with best refractive correction as determined from cycloplegic refraction.

2.4. Enrollment of Eligible Patients

Eligible patients can be enrolled either by entering the Enrollment Form on the PEDIG website or by faxing the form to the Jaeb Center if internet access is down. Each enrolled patient will be assigned a unique identifier number.

2.5. Prescribing Spectacles

2.5.1. Spectacle Correction

The following spectacle correction should be prescribed:

- Full correction of anisometropia
- Full correction of myopia
- Full correction of astigmatism
- Hypermetropia either fully corrected or symmetrically reduced by up to +1.50 D

Note: Contact lenses should not be prescribed, as their use will not be permitted during the study.

2.5.2. Obtaining Spectacles

- Patients will be sent to an optician to have the spectacles made. Spectacles will be paid for by the study and will be made preferably by a study-certified optician who will bill the study an agreed-upon amount for the spectacles.
- The spectacles will either be sent directly to the investigator or will be picked up by the patient on the day of the Spectacle Baseline Visit. The new spectacles should not be worn prior to the Spectacle Baseline Visit.

2.6 Scheduling the Spectacle Baseline Visit

The patient will return for a Spectacle Baseline Visit within 30 days after the Enrollment Visit. The Spectacle Baseline Visit needs to be scheduled such that the spectacles prescribed at enrollment will be available, as trial frames or phoropter are not to be used for visual acuity testing at the Spectacle Baseline Visit.

Although it is preferable to complete the Spectacle Baseline Visit at least one day after the Enrollment Visit, the visits may be completed on the same day if both of the following are met:

- The new spectacles are available at the visit and have not been previously worn
- The patient has not been cyclopleged prior to visual acuity testing

If the Enrollment Visit and the Spectacle Baseline Visit occur on the same day, visual acuity need only be tested once provided the patient is wearing the new spectacles for the testing.

CHAPTER 3: SPECTACLE BASELINE VISIT

3.1. Introduction

The patient will return for a Spectacle Baseline Visit within 30 days after the Enrollment Visit.

The Spectacle Baseline Visit needs to be scheduled such that the spectacles prescribed at enrollment will be available, as trial frames or phoropter are not to be used for visual acuity testing at this visit. Prior to the visit, the office staff should verify that the spectacles prescribed at enrollment either have been received or that the patient will be picking them up on the day of this visit.

3.2. Verification of Spectacles

Prior to testing acuity, the spectacles prescription should be verified with a lensometer. Spherical power must be within 0.25 D of the prescribed correction. If the prescribed cylinder correction is ≥1.0 D, then the cylinder axis must be within 5 degrees of the prescribed correction; if the prescribed cylinder correction is <1.0 D, then the cylinder axis must be within 10 degrees of the prescribed correction.

- If these criteria are not met, the spectacles must be re-made and the patient will return at a later date for the Spectacle Baseline Visit (see section 3.5). Therefore, if possible, it is best if the spectacle prescription is verified with a lensometer prior to the patient's visit.

If the spectacles are not brought to the visit, the patient should return with the spectacles at a later date for the Spectacle Baseline Visit. In the meantime the patient should not begin wearing the spectacles.

3.3. Examination Procedures

Testing at the visit will include:

1. Binocular and monocular visual acuity testing with the patient wearing the new spectacles, without cycloplegia, and using the same testing method used at enrollment
   - The patient should wear the new spectacles for 10 to 30 minutes before visual acuity is tested.
   - The binocular acuity test should be performed first, followed by monocular testing of the right eye and then the left eye.
2. An assessment of ocular motility and alignment with the Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near
   - If patient's visual acuity is too poor to fixate for SPCT, a modified Krimsky test should be performed.
   - The standard protocols for these procedures are described in the PEDIG Testing Procedures Manual.
3. Binocularity testing with Randot Preschool Test (testing procedures in PEDIG testing Procedures Manual)

3.4. Visual Acuity Reduced from Enrollment Visit

3.4.1. Patients Prescribed Hyperopic Correction at Enrollment

In a patient whose new spectacles contain hyperopic correction, if the acuity at the Spectacle Baseline Visit in either eye is reduced from the Enrollment Visit (or from the last visit if Enrollment and Spectacle Baseline Visit are being completed on the same day) by 5 or more letters in patients tested using E-ETDRS testing or by one or more lines in patients testing using ATS HOTV testing, the possibility that the reduced acuity is due to incomplete relaxation of accommodation should be considered.

In cases of incomplete relaxation of accommodation, the acuity should be retested with a –1.00 D lens over the spectacles.

- If a minus lens improves visual acuity:
  - The acuity obtained with the minus lens should be recorded on the exam form and it should be noted on the form that a minus lens was used.
  - It is at investigator discretion whether to change the spectacles at this time or to allow the patient time to relax into them. At the 5-week visit, if the acuity has not improved to at least the level obtained with the minus lens at the Spectacle Baseline Visit, it is recommended that the spectacles should be changed if they weren't changed at the baseline visit.
- If a minus lens does not improve visual acuity:
  - The patient can begin the study unless the investigator suspects an error in refraction, in which case the cycloplegic refraction may be repeated. If spectacles are changed, the patient should return for the Spectacle Baseline Visit at a later date (see section 3.5).

3.4.2. Patients Not Prescribed Hyperopic Correction at Enrollment

If the spectacles do not contain hyperopic correction, and incomplete relaxation of accommodation is not suspected, then the visual acuity test should be repeated. If the reduction in visual acuity persists on the second test, then the refraction should be checked with cycloplegia. If spectacles are changed, the patient should return for the Spectacle Baseline Visit at a later date (see section 3.5).

3.5. Changing Spectacles

When spectacles with optimal correction are not available at the Spectacle Baseline Visit whether due to the spectacles having been made incorrectly or due to a new correction being prescribed, the patient should not wear any spectacles until he or she returns at a later date for the Spectacle Baseline Visit with the new spectacles.

3.6. Continuation of Follow Up

The following patients will be ineligible for follow up and will have completed the study:

- Patients whose monocular acuity measured at the Spectacle Baseline Visit is 20/25 or better in both eyes
- Patients who wore the new spectacles prior to the day of the Spectacle Baseline Visit
- Patients who received unilateral amblyopia treatment prior to the Spectacle Baseline Visit

All other patients will begin one year of follow up and will return for the first follow-up visit in 5(±1) weeks.

CHAPTER 4: FOLLOW-UP VISITS

4.1. Visit Schedule

Patients eligible for study follow up will have visits at 5±1 week, 13±2 weeks, 26±4 weeks, and 52±4 weeks.

- If at the 5-week or 13-week visit the patient's monocular visual acuity is 20/25 or better in each eye, all subsequent visits prior to the 52-week visit may be skipped, and the patient should return for the 52-week visit.

Patients may have additional exams at investigator discretion.

4.2. Examination Procedures

4.2.1. Visual Acuity Testing

At each follow-up visit, visual acuity will be tested both binocularly and monocularly, without cycloplegia. The binocular test should be performed first, followed by monocular testing of the right eye and then the left eye.

- Patients who were tested using ATS HOTV at the Enrollment and Spectacle Baseline Visits will be tested with ATS HOTV throughout the study.
- Patients who were tested using E-ETDRS at the Enrollment and Spectacle Baseline Visit will be tested with E-ETDRS throughout the study.

Note: If visual acuity worsens or fails to improve, additional tests may be performed as part of a standard care work-up. The results of any additional testing should be recorded on the Follow-up Examination Form.

4.2.1.1. Retesting of Visual Acuity

Binocular acuity and the appropriate monocular visual acuity *should* be retested with best refractive correction using trial frames or phoropter in the following situations:

1. A manifest or cycloplegic refraction is performed at the visit and the results indicate that the current spectacles violate any of the following criteria:
   - Spherical equivalent and cylinder within 0.50 D of fully correcting anisometropia
   - Cylinder power is within 0.50 D of fully correcting the astigmatism
   - Cylinder axis in both eyes is within 5 degrees of the axis in the spectacles when cylinder power is ≥ 1.00 D and within 10 degrees of the axis in the spectacles when cylinder power is < 1.00 D
   - Hypermetropia is either fully corrected, undercorrected by up to +1.50 D, or overcorrected by up to 0.50 D
   - Myopia is either fully corrected, undercorrected by up to +.25 D, or overcorrected by up to 0.50 D

2. Acuity is reduced from the previous visit in an eye treated with atropine for unilateral amblyopia in the other eye.

4.2.2. Additional Testing at 52-Week Visit

In addition to visual acuity testing, binocularity will be tested with the Randot Preschool Test at the 52-week follow-up visit.

A refraction (manifest or cycloplegic) will also be done at this visit. If the refraction indicates a substantial change from the patient's current spectacles, the appropriate visual acuities should be retested with trial frames or phoropter (see section 4.2.1.1).

If the monocular visual acuity in either eye is worse than 20/25 at this visit, the presumed cause of visual loss will be recorded on the Follow-up Examination Form.

4.3. Unilateral Amblyopia Treatment

Treatment for unilateral amblyopia will be at investigator discretion, however, the suggested guideline is that unilateral amblyopia treatment be initiated only once monocular visual acuity has stopped improving in both eyes.

Any unilateral amblyopia treatment that is prescribed should be recorded on the exam form.

If the patient is being treated with atropine, atropine must be discontinued at least 2 weeks prior to the 52-week visit.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS IN FOLLOW UP

5.1. Maintaining Patient Follow Up

The Jaeb Center may contact the parents or guardian of each patient if needed to help coordinate scheduling of examinations. Permission for such contacts will be included in the Informed Consent Form.

5.2. Patient Withdrawals

A patient (and in this case the parents or guardian) may withdraw from the trial at any time. This is expected to be a very infrequent occurrence in this trial in view of the study design's similarity to routine clinical practice. If the parents or guardians indicate that they want to withdraw the 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, 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 can be performed at any time the investigator suspects that refractive error may not be optimally corrected. It is also at investigator discretion whether to change the spectacle correction if the refraction indicates a change.

5.4. Management of Strabismus

Strabismus surgery is allowed at the discretion of the clinician. Performance of such strabismus surgery will be reported on the Follow-up Examination Form. After surgery, the patient should continue wearing his/her spectacle correction.

5.5. Intercurrent Events

1. If visual acuity should worsen, the investigator should evaluate this condition using best clinical judgment and perform whatever work up is clinically indicated to assess for an alternate cause (i.e., other than amblyopia) for the visual loss. Patients found to have a cause other than amblyopia that fully explains the visual loss (i.e., amblyopia was never present) will be discontinued from the study. This will be reported on the Patient Final Status Form.
2. Eye injuries or development of eye problems that might affect vision will be reported on the Follow-up Examination Form. Likewise, development of a serious medical problem that might affect study participation or testing results by the affected patient will be recorded.

5.6. Risks of Examination Procedures

The procedures in this study are part of daily ophthalmic 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.

CHAPTER 6: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

6.1. Sample Size Estimation

The sample size has not been statistically computed for this study. It is anticipated that enrollment will remain open until 100 patients have been recruited. At least 50 patients will be enrolled who have an interocular difference of less than 3 lines by ATS HOTV or less than 15 letters by E-ETDRS at the Spectacle Baseline visit.

Table 1 indicates the expected widths of 95% confidence interval for mean visual acuity improvement for 100 patients for various standard deviations.

Table 1. Expected 95% Confidence Interval for Mean Improvement in Binocular Visual Acuity at 52 Weeks for Sample Size of 100 Patients

Mean Improvement in Binocular Visual Acuity at 52 Weeks *(logMAR)*	**Standard Deviation *(logMAR)***		
	.11	**.14**	**.18**
.05	.03 - .07	.02 - .08	.02 - .09
.1	.08 - .12	.07 - .13	.07 - .14
.15	.13 - .17	.12 - .18	.12 - .09
.20	.18 - .22	.17 - .23	.17 - .24
.25	.23 - .27	.22 - .28	.22 - .29
.30	.28 - .32	.27 - .33	.27 - .34

Cells contain 95% confidence intervals for mean improvement in binocular visual acuity in logMAR units.

6.2. Statistical Analysis

The analytic objectives include (1) to determine the amount of binocular visual acuity improvement with treatment and (2) to determine the time course of binocular visual acuity improvement with treatment.

The primary outcome measure will be mean improvement in binocular visual acuity at 52 weeks. Binocular visual acuity is chosen as the primary outcome measure because it best represents visual acuity in the "real world" setting. Also, a few patients will have latent nystagmus and may test worse with monocular than binocular visual acuity tests, therefore binocular results are more reflective of their functional visual acuity in daily life.

A secondary analysis will parallel the primary analysis but will include only patients treated with spectacles alone throughout the entire 52-week period.

For each patient, the maximum improvement will be computed and the visit at which this occurred will be identified. Descriptive statistics will include determinations of the distribution of number of lines of maximum improvement stratified by baseline level of visual acuity and the cumulative distribution of the proportion of patients reaching maximum improvement at each visit.

CHAPTER 7: REFERENCES

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