AMBLYOPIA TREATMENT STUDY

ATS5

A Randomized Trial to Evaluate 2 Hours of Daily Patching for Amblyopia in Children 3 to <7 Years Old

PROTOCOL

Version 1.0

May 12, 2003

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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. Objectives and Rationale

This study is addressing issues related to the treatment of amblyopia in children 3 to <7 years old with visual acuity 20/40 to 20/400. The study consists of two phases: (1) a *Spectacle Phase* in which patients are prescribed spectacles and followed until maximal improvement in visual acuity has occurred and (2) a *Randomized Trial* comparing a group using patching treatment (in addition to spectacle correction) with a control group using spectacle correction only.

1.1.1. Spectacle Phase

The objectives of the *Spectacle Phase* are as follows:

1. In previously untreated pure anisometropic patients (i.e. patients who have not used spectacles in the last year and who do not have strabismus), to determine (1) the incidence of resolution of amblyopia with spectacle correction alone and (2) the time course of visual acuity improvement with spectacle correction alone
2. In all other patients (i.e. patients [1] who have strabismus, [2] who have combined mechanism amblyopia, or [3] who have anisometropia only but have worn spectacle correction within the last year], to achieve maximal improvement with spectacle correction prior to entering the randomized trial

   Note: The following patients will skip the Spectacle Phase and will enter the Randomized Trial directly:

   - Patients with strabismus or combined mechanism amblyopia who either do not need spectacle correction or who have been wearing the proper correction for at least 16 weeks
   - Patients with anisometropia only who have been wearing the proper correction for at least 16 weeks

As part of screening for the study, the patient's refractive error will be measured. The study will pay for spectacles for patients requiring a new refractive correction (new spectacles for patients who have not been wearing spectacles or a change in spectacle correction for patients already wearing spectacles). These patients, as well as patients who are currently wearing optimal spectacle correction but have been doing so for less than 16 weeks, will enter the *Spectacle Phase* of the study and will be followed until either the amblyopia resolves or until the amblyopic eye stops improving. Patients who still meet study criteria for amblyopia will then move into the *Randomized Trial Phase* of the study.

There are few data on the improvement that occurs with spectacle correction alone in cases of anisometropic amblyopia. The only published study of which we are aware is that of Moseley, et al,[1] who found that 8 of 12 patients prescribed spectacles for the first time improved 3 or more lines in the amblyopic eye. Therefore, the current study will provide important information related to the management of patients with anisometropic amblyopia.

1.1.2. Randomized Trial

The principal objectives of the randomized trial are:

1) To determine whether 5 weeks of patching treatment (2 hours of patching per day of the sound eye combined with at least one concurrent hour of near activities) compared with a control group (using spectacle correction only) improves visual acuity in patients with moderate to severe amblyopia (20/40 to 20/400)

2) To determine the maximal improvement and time course of improvement with this patching treatment regimen

Despite clinical experience that strongly indicates that amblyopia can be improved with treatment, there are those who claim that the benefit of treatment is unproven. Although improvement with amblyopia therapy has been shown in prospective trials, there have been no conclusive data published from a randomized trial evaluating the effect of amblyopia treatment compared with a control group. Therefore, we have designed a randomized trial to definitively address this issue.

In the trial, the effect on amblyopic eye acuity after five weeks of 2 hours of prescribed daily patching (combined with at least one hour of concurrent near activities) will be compared with a control group using spectacle correction only. In a study conducted by the Pediatric Eye Disease Investigator Group, a 2-hour daily patching treatment regimen improved moderate amblyopia (20/40 to 20/80) by an amount similar to the improvement seen with 6 hours of daily patching.

At the end of five weeks, patients whose amblyopic eye has improved from baseline will continue in follow up, using the assigned treatment, until the amblyopic eye acuity stops improving or until the amblyopia resolves. This will provide data on the maximum improvement achievable with this treatment regimen and on the time course to reach maximal improvement.

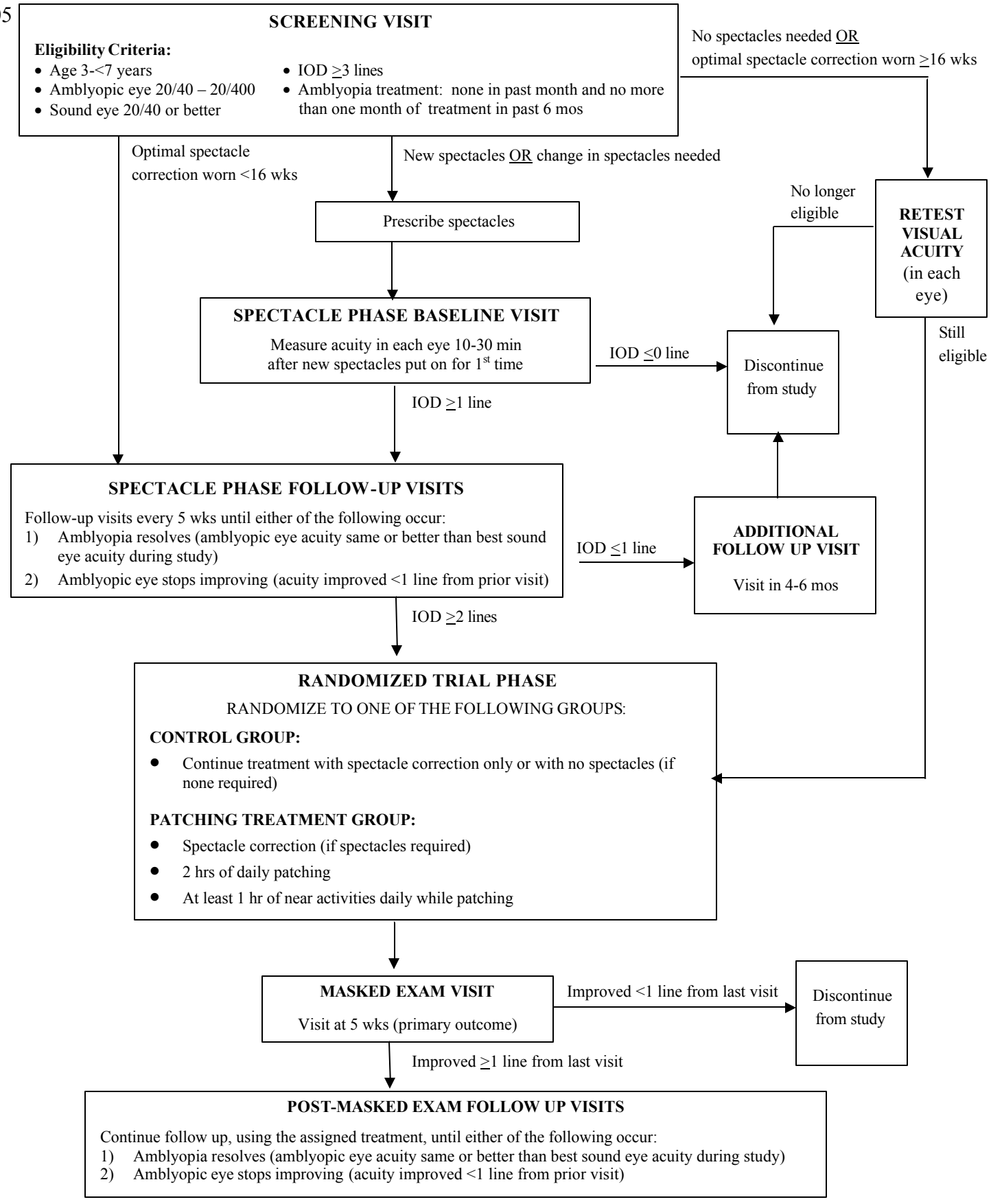
The sample size for the primary analysis for the randomized trial has been estimated to be 134 patients. Patients will be enrolled into the Spectacle Phase until the recruitment goal for the Randomized Trial is reached.

There is no known harm in deferring treatment of amblyopia for five weeks in the age range to be included in the trial (3 to <7 years old). Standard care for a patient with amblyopia includes prescribing spectacle correction and having the patient return in 4 to 6 weeks for measurement of visual acuity. Spectacles alone are continued as long as the acuity in the amblyopic eye is improving. Once the acuity stops improving, occlusion or other active treatment is initiated. The maximum delay in active treatment of the control group beyond the standard of care is 5 weeks. In our prior Amblyopia Treatment Study protocols on patients in this age range, we have found no indication that the response to patching treatment is related to age. Therefore, it is highly unlikely that a delay in initiating treatment of weeks or even months could be harmful.

References

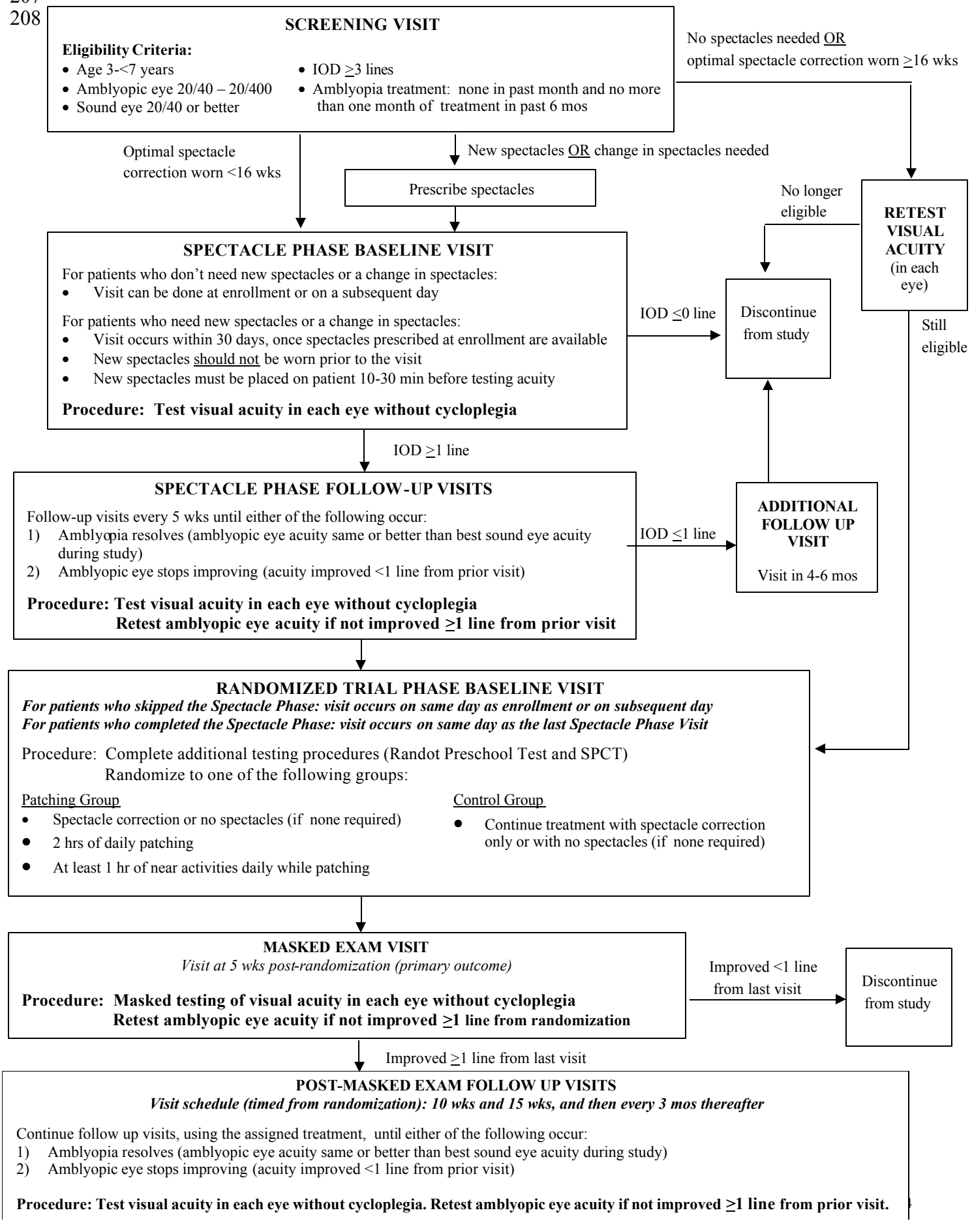
1. Moseley MJ, Neufeld M, McCarry B, Et al. Remediation of refractive amblyopia by optical correction alone. Ophthal Physiol Opt 2002; 22:296-9.

1.2. Study Summary Flowchart



Note: IOD defined as amblyopic eye acuity minus sound eye acuity.

1.3. Study Detail Flowchart



CHAPTER 2: SCREENING VISIT

At the screening visit, eligibility is assessed and spectacles are prescribed if indicated (paid for by the study).

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 (Spectacle and Randomized Trial phases) 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 patient brochure and 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 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 using the ATS single-surround HOTV protocol

3. Amblyopia associated with strabismus (comitant or incomitant), anisometropia, or both
   - Criteria for strabismus: At least one of the following criteria must be met:
     - Heterotropia at distance and/or near fixation on examination (with or without spectacles)
     - History of strabismus surgery (or botulinum)
     - Documented history of strabismus which is no longer present (and which in the judgment of the investigator is the cause of amblyopia)

   - Criteria for anisometropia: At least one of the following criteria must be met:
     - ≥0.50 D difference between eyes in spherical equivalent
     - ≥1.50 D difference between eyes in astigmatism in any meridian

   - Criteria for combined mechanism amblyopia: Both of the following criteria must be met:
     - Criteria for strabismus are met (see above)
     - ≥1.00 D difference between eyes in spherical equivalent or ≥1.50 D difference between eyes in astigmatism in any meridian
       - Note: the spherical equivalent requirement differs from that in the definition for refractive/anisometropic amblyopia.

4. Visual acuity, measured in each eye according to the procedures described in section 2.3.2, meeting the following criteria:
   - Visual acuity in the amblyopic eye 20/40 to 20/400 inclusive
   - Visual acuity in the sound eye ≥20/40
   - Inter-eye acuity difference ≥3 logMAR lines (i.e. amblyopic eye acuity at least 3 lines worse than sound eye acuity)

5. No amblyopia treatment (other than spectacles) in the past month and no more than one month of amblyopia treatment in the past 6 months
   - Any treatment more than 6 months prior to enrollment is acceptable

6. No current vision therapy or orthoptics

7. No ocular cause for reduced visual acuity
   - Nystagmus per se does not exclude the patient if the above visual acuity criteria are met

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

9. No myopia more than a spherical equivalent of -6.00 D

10. No prior intraocular or refractive surgery

11. No known skin reactions to patch or bandage adhesives

12. Parent understands protocol and, if child is eligible to enter randomized trial, parent is willing to accept randomized treatment

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

14. Relocation outside of area of an active ATS site within next six 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), spectacle correction, and history of allergy/intolerance to bandage adhesive.

2.3.2. 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 (or study-approved alternative instrument). The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual. Aspects of the testing protocol that are specific to this study are indicated below:

1. Testing is done with best refractive correction.
   - For patients with refractive error who either do not have spectacles or whose spectacles do not fully correct the refractive error (as described in section 2.5.1), testing will be done with trial frames or a phoropter**.**
2. Testing can be done 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 done 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, then acuity can be tested with current spectacles (or no spectacles) and the patient can be enrolled if the investigator believes that it is likely the patient would be eligible if tested with the optimal refractive correction.

2.3.3. Other Testing

Additional testing that will be completed as part of the patient's usual care will include an assessment of ocular motility and alignment using the Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near, recording of the presence of primary position nystagmus (with and without monocular occlusion), a cycloplegic refraction, and an ocular examination.

- Any of these additional procedures that have been performed within the prior 2 months do not need to be repeated at time of enrollment.
- If patient's visual acuity is too poor to fixate for SPCT, a modified Krimsky test should be performed.
- The standard protocol for each procedure is described in the ATS Testing Procedures Manual.

2.4. Enrollment of Eligible Patients

A patient can be enrolled either by entering the Enrollment Form on the ATS website or by faxing the Enrollment Form to the Jaeb Center. Each enrolled patient will be assigned a unique identifier number.

2.5. Prescribing Spectacles

2.5.1. Spectacle Correction

The study will provide new spectacles for patients who are being prescribed spectacles for the first time or who require a change in refractive correction.

The following guidelines will apply in prescribing spectacles.

2.5.1.1. Patients Meeting Criteria for Anisometropic Amblyopia

For patients meeting the anisometropia criteria in section 2.2 (i.e., there is $\geq$ 0.50 D difference between eyes in spherical equivalent or $\geq$ 1.50 D difference between eyes in astigmatism, with or without strabismus), guidelines for prescribing spectacles vary depending on whether the patient has previously worn spectacles within the last 12 months.

2.5.1.1.1. Anisometropic Patients Without Prior Spectacle Use

For patients without prior spectacle use (defined as no spectacle wear in previous 12 months), the following spectacle correction should be prescribed:

- Full correction of anisometropia
- Full correction of astigmatism
- Hypermetropia >3.00 D either fully corrected or symmetrically reduced by up to +1.50 D
- Myopia $\geq$0.50 D fully corrected in the both eyes

2.5.1.1.2. Anisometropic Patients Currently Wearing Spectacles

For patients currently wearing spectacles, a new prescription is not necessary as long as the current spectacles meet the following criteria:

- Spherical equivalent and cylinder are within 0.50 D of fully correcting the anisometropia
- Cylinder power must be within 0.75 of fully correcting the astigmatism.
- Cylinder axis in both eyes is within 10 degrees of the axis in the spectacles when cylinder power is $\geq$ 1.00 D (if cylinder power is < 1.00 D, spectacle change is at the investigator's discretion)
- Hypermetropia >3.00 D is either fully corrected or reduced symmetrically by up to +1.50 D

2.5.1.2. Patients with Strabismic Amblyopia or Combined Mechanism Amblyopia

- For patients meeting the criteria for strabismus only or for combined mechanism amblyopia, the same criteria listed in 2.5.1.1.2 will apply.

2.5.2. Obtaining Spectacles

For patients who are being prescribed spectacles for the first time or who require a change in spectacle correction:

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

2.6. Scheduling of the Next Visit

2.6.1. Patients Skipping the Spectacle Phase

The following patients will skip the Spectacle Phase of the study and will directly enter the Randomized Trial (see chapter 4):

- Patients who do not require spectacle correction
- Patients who have worn optimal spectacle correction for at least the prior 16 weeks

The Randomization Visit can be performed either the same day (provided all testing can be completed according to the protocol-specified state of cycloplegia) or on a subsequent day.

- If the patient is being evaluated for randomization on the same day that the Screening Exam was performed, acuity will be retested for the Randomized Trial even though it was already measured once on this day.
    - If on retesting prior to randomization the visual acuity in either eye does not still meet eligibility criteria (amblyopic eye between 20/40 and 20/400 inclusive and sound eye 20/40 or better), the patient will not be randomized, the remaining testing for the Randomization Visit will not be completed, and the patient will be discontinued from the study.

2.6.2. Patients Entering the Spectacle Phase

All patients who are entering the Spectacle Phase (see section 2.6.1 for criteria for skipping the Spectacle Phase) will have a Spectacle Phase Baseline Visit within 30 days after the Screening Examination. The visit needs to be scheduled such that the spectacles prescribed at enrollment will be available, as trial frames are not to be used for visual acuity testing at the Spectacle Phase Baseline Visit.

Patients who are currently wearing optimal spectacle correction but for less than 16 weeks may complete both the Screening Exam and Spectacle Phase Baseline Visit on the same day provided all testing can be completed according to the protocol-specified state of cycloplegia (see section 3.2).

CHAPTER 3: SPECTACLE PHASE

3.1. Introduction

The purpose of the Spectacle Phase is for each patient to achieve maximum improvement in the amblyopic eye acuity that can be achieved with spectacles alone.

3.2. Spectacle Phase Baseline Visit

Patients who at the Screening Exam are wearing optimal spectacle correction but have been doing so for less than 16 weeks may complete the Spectacle Phase Baseline Visit on the same day provided all testing can be completed according to the protocol-specified state of cycloplegia (refer to sections 2.3 and 3.2.1)

Patients who needed new spectacles or a change in spectacles will return for the Spectacle Phase Baseline Visit within 30 days after the Screening Examination.

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 the Spectacle Phase Baseline Visit.

At the visit, the spectacles prescription should be verified with a lensometer. Sphere and cylinder power must be within 0.25 D and cylinder axis 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 Phase Baseline Visit (see section 3.2.2).

3.2.1. Visual Acuity Testing

Visual acuity is measured in each eye at distance without cycloplegia and using the ATS HOTV visual acuity testing protocol with the EVA tester (or approved alternative).

Patients who are receiving spectacles for the first time or who had a change in spectacle correction should wear the new spectacles for 10 to 30 minutes before visual acuity is tested.

If the amblyopic eye acuity is now the same or better than the sound eye acuity, the patient's study participation will end.

- If the sound eye acuity is worse than it was at the Screening Exam, it should be retested before this judgment is made.

If the amblyopic eye acuity is still at least one line worse than the sound eye acuity:

- If amblyopic eye acuity is the same or better than it was at the Screening Exam Spectacle Phase, follow up will begin immediately.
- If amblyopic eye acuity is worse than it was at the Screening Exam, refer to section 3.2.1.1. for instructions on whether spectacles should be changed and when Spectacle Phase Follow up should begin.

3.2.1.1. Visual Acuity Reduced from Enrollment Visit

3.2.1.1.1. Presumed Latent Hyperopia

If the acuity at the Spectacle Phase Baseline Visit <u>in either eye</u> is reduced by one line or more from the Enrollment Visit in a patient who was given new spectacles with hyperopic correction (or a change in spectacles with a substantial increase in the hyperopic correction), the possibility that the reduced acuity is due to latent hyperopia should be considered.

In cases of presumed latent hyperopia (i.e., persistent accommodative tone), the acuity should be retested with –1.00 D lens.

- If 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 refraction should be repeated, and if found to be different, the spectacles should be changed and the patient should return for the Spectacle Phase Baseline Visit at a later date (see section 3.2.2).
- If a minus lens improves visual acuity:
    - If the patient is a previously untreated pure anisometrope (i.e. must be without prior spectacle use in the last year and must not have strabismus), the spectacles should be changed, reducing the plus, and the patient should return for the Spectacle Phase Baseline Visit at a later date (see section 3.2.2).
    - If the patient is *not* a previously untreated pure anisometrope, the investigator can either change the spectacles or wait and allow the patient to relax into them.
        - If at the 5 week visit visual acuity has not improved to at least the acuity obtained using the minus lens at baseline and the spectacles haven't already been changed, the spectacles should be changed at this time if an overrefraction and visual acuity testing confirm a better visual acuity with a change in refraction.

3.2.1.1.2. Other Cases of Reduced Visual Acuity

If the acuity at the Spectacle Phase Baseline Visit in either eye is reduced by one line or more from the Enrollment Visit, and presumed latent hyperopia is not suspected, the refraction should be checked with cycloplegia.

- If the original refraction was correct, the acuity obtained will be the acuity for the Spectacle Phase Baseline Visit.
- If the original refraction was not correct, the spectacles should be changed, and the patient should return for the Spectacle Phase Baseline Visit at a later date (see section 3.2.2).

3.2.2. Changing Spectacles

When spectacles with optimal correction are not available at enrollment whether due to the spectacles having been made incorrectly or due to a new correction needing to be prescribed, while the spectacles are being changed, the patient should not wear the spectacles prescribed at enrollment. In the meantime the patient should either wear his/her previous spectacles or wear no spectacles (as appropriate) until he or she returns at a later date for the Spectacle Phase Baseline Visit with the new spectacles.

3.3. Spectacle Phase Follow-up Visits

Patients whose amblyopic eye acuity is one or more lines worse than sound eye acuity at the Spectacle Phase Baseline Visit will begin Spectacle Phase Follow Up.

Follow-up visits occur every 5 weeks (±1 week) as long as both of the following criteria are met:

- Amblyopic eye is improving, defined as improvement of one or more lines from the prior visit
- Amblyopia is still present, defined as amblyopic eye acuity at least one line worse than the best sound eye acuity that has been recorded at any visit during the study

Note: If the amblyopic eye acuity meets the above criteria, follow up will continue even if the sound eye acuity has worsened from the prior visit.

At each follow up visit, visual acuity will be tested in both eyes without cycloplegia and using the ATS HOTV visual acuity testing protocol with the EVA tester (or approved alternative). If the amblyopic eye acuity has not improved from the prior visit, acuity should be retested.

- If on the retest there is still no improvement from the prior visit, then the patient has completed the Spectacle Phase of the study, otherwise, the patient continues in follow up.

3.4. Follow Up After the End of the Spectacle Phase

When the Spectacle Phase of the study is over, the patient's next follow up visit depends on his/her inter-ocular difference.

- Patients who have an inter-ocular difference of $\leq$1 line will continue using spectacle correction only and will have a follow up visit 4-6 months after the last Spectacle Phase visit, then will be discontinued from the study.
- Patients who have an inter-ocular difference of $\geq$2 lines will enter the Randomized Trial Phase of the study.

Note: Throughout this protocol, inter-ocular difference is defined as the amblyopic eye acuity minus the sound eye acuity.

CHAPTER 4: RANDOMIZED TRIAL PHASE

4.1. Assessment of Eligibility for the Randomized Trial

4.1.1. Patients Who Completed the Spectacle Phase

Eligibility for the randomized trial is assessed at the last visit in the Spectacle Phase (see section 3.4).

- The eligibility criterion for the Randomized Trial is an inter-ocular difference of 2 or more lines.
  - The better of the two amblyopic eye visual acuity testings at the last visit of the Spectacle Phase serves as the baseline amblyopic eye acuity for the Randomized Trial.

4.1.2. Patients Who Skipped the Spectacle Phase

For patients who skipped the Spectacle Phase (see section 2.6.1), visual acuity will be tested in each eye using the ATS HOTV visual acuity testing protocol. This testing must be performed without cycloplegia and with the patient wearing spectacles if they have been prescribed (i.e. trial frames cannot be used).

- If the patient is being evaluated for randomization on the same day that the Screening Exam was performed, amblyopic eye acuity will be retested even though it was already measured once on this day.
  - If on retesting prior to randomization the visual acuity in either eye does not still meet eligibility criteria (amblyopic eye between 20/40 and 20/400 inclusive and sound eye 20/40 or better), the patient will not be randomized, the remaining testing for the Randomization Visit will not be completed, and the patient will be discontinued from the study.
- The better of the two visual acuity testings will serve as the baseline acuity for the Randomized Trial.

4.2. Additional Randomized Trial Baseline Testing

The following additional tests will be performed at this visit:

- Randot Preschool test
- Measurement of ocular deviation in primary position at distance and near by Simultaneous Prism and Cover Test (SPCT) (see ATS Testing Procedures manual)

4.3. Randomization Groups

Each patient will be randomly assigned to one of two treatment groups:

- **Patching Group:** Spectacle correction (if prescribed) and 2 hours of daily patching
  - During at least one hour of the patching and while wearing spectacles (if prescribed), the patient should perform near visual activities as described in section 4.3.1, #5.
- **Control Group:** Spectacle correction only or no spectacles if none are required

The Jaeb Center will construct a Master Randomization List stratified by site for patients with amblyopic eye visual acuity 20/40 to 20/100 with IOD $\geq$3 lines. Other patients will be stratified overall (not by site) for (1) amblyopic eye acuity 20/125 to 20/400 with IOD $\geq$3 lines and (2) IOD $\geq$2 lines).

4.3.1. Patching Group

1. Patching will be performed using commercially-available patches, which will be provided by the study. If skin sensitivity occurs, an alternative brand of patch will be provided. If no skin

patch is tolerated, a felt "Patch-Works" type patch will be placed on the lens of glasses over the sound eye; if glasses are not being worn, then plano glasses will be provided.

2. The two hours of daily patching should be continuous. Also, parents will be instructed not to count periods when the child is sleeping as patching time.

3. If a patient is noncompliant with treatment, the parents should be encouraged to persist with the treatment to the best of their ability.

4. Prior to the 5-week masked exam, patients should not be prescribed additional hours of occlusion or other therapies for amblyopia. If the parent requests such a change, then every attempt should be made to complete the 5-week masked exam prior to changing treatment, even if it needs to be completed early.

5. The parent will be instructed to have the child spend at least one hour of patching time each day doing eye-hand coordination activities at near, such as crafts, coloring, tracing, cutting out objects, dot-to-dot connecting, hidden pictures and word finds, computer-generated or video games (e. g. Game Boy/Nintendo/PlayStation), computer/internet, reading, written homework assignments, or other activities requiring eye-hand coordination. During the remaining time, the child can perform his or her usual activities other than certain activities such as riding a bike, which could be dangerous. Office-based vision therapy will not be used during the study.

6. A home calendar log will be used to record treatment received.

   - The child will place an adhesive sticker on the log on days when the protocol treatment was successfully completed. The caregivers will be asked to indicate daily the number of hours of patching completed and the time spent performing near activities during patching.

   - These logs will be turned in to the investigator at each of the protocol visits. At the 5-week visit, the logs will be reviewed. The investigator's assessment of compliance will be recorded on the Follow-up Examination Form.

4.3.2. Control Group

1. Prior to the 5-week masked exam, the Control Group should be prescribed no treatment for amblyopia other than spectacle correction (if applicable).

2. If the parent requests that the child be started on active amblyopia treatment, then an attempt should be made to complete a masked exam prior to the patient's starting on the treatment.

3. If a patient receives active treatment of any kind for one week or more, the patient will end study follow up.

4.4. Primary Outcome Examination

The first follow up visit in the Randomized Trial Phase is the primary outcome exam at 5±1 weeks.

4.4.1. Masked Visual Acuity Testing

At this visit, visual acuity testing will be performed by a certified masked examiner using the ATS HOTV visual acuity testing protocol. The right eye will be tested first, followed by the left eye.

If amblyopic eye acuity is not at least one line better than the Randomized Trial Phase baseline acuity, the amblyopic eye will be retested (either by the same masked examiner or by a different examiner).

The first amblyopic eye acuity from the masked examiner testing will be considered the primary outcome measure for the Randomized Trial.

4.4.2. Additional Testing at Primary Outcome Examination

The following additional testing will be completed at the primary outcome examination:

1) Randot Preschool Test
2) Measurement of ocular deviation with Simultaneous Prism and Cover Test (SPCT)

4.5. Continued Follow Up After the Primary Outcome Exam

If at the 5-week primary outcome visit the amblyopic eye acuity has not improved at least 1 line from the Randomized Trial Phase baseline acuity or if the amblyopia has resolved (amblyopic eye acuity same or better than best sound eye acuity during study), the patient will discontinue study follow up and treatment will be at investigator discretion.

If at the 5-week primary outcome visit the amblyopic eye acuity has improved 1 or more lines from the Randomized Trial Phase baseline acuity and the amblyopia is still present (amblyopic eye acuity worse than best sound eye acuity during study), the patient will continue in the study.

4.5.1. Treatment During Continued Follow Up

Patients continue using the randomization-assigned treatment

- Patients in the Patching Group will continue using 2 hours of patching per day (including at least one hour of near activities during patching) in addition to continuing to spectacle correction (if required).
- Patients in the Control Group will continue spectacle correction only (or no spectacles if none are required).

4.5.2. Continued Follow Up Visit Schedule

Patients will have follow-up visits according to the visit schedule below as long as both of the following criteria are met:

- Amblyopic eye is improving, defined as improvement of one or more lines from the prior visit
- Amblyopia is still present, defined as amblyopic eye acuity at least one line worse than the best sound eye acuity that has been recorded at any visit during the study

The follow up visit schedule is a visit at 10±1 weeks, 15±1 weeks, and then at least once every three months thereafter.

At each follow up visit, visual acuity will be tested.

- If the visual acuity has not improved at least one line from the prior visit, it will be retested and the better of the two acuities will be used to determine whether the patient should continue follow up or be discontinued 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 or guardian 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.

- One phone contact is planned to take place during the first month after enrollment. 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 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 guardian 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.

5.4. Management of Strabismus

Strabismus surgery is allowed at the discretion of the clinician. These will be recorded in the comment section of the Follow-up Examination Form.

5.5. Risks of Patching

The risks involved in the study are identical to those that would be present for a patient treated with occlusion therapy with patching who is not participating in the study.

In view of the small number of hours of daily patching, significant skin irritation is unlikely. If irritation occurs, the parent will be advised to put an emollient on the skin and discontinue use of the patch for a day.

If a skin reaction to the patch occurs, or an allergic reaction occurs serious enough to discontinue patching, the investigator should call his or her assigned Steering Committee member to discuss the case. An alternative adhesive patch may be tried. If patching with adhesive patches is discontinued, then the patient should be tried with Patch Works on glasses (or on plano lens if patient not wearing spectacles).

Patching potentially could decrease the visual acuity in the sound eye, although this is almost always reversible. However, this occurrence is extremely unlikely in view of the small number of hours of daily patching. The diagnosis and management of reverse amblyopia is left to the investigator's judgment.

Patching could precipitate the development of an ocular deviation. If treatment precipitates the development of an ocular deviation (e.g., esotropia in child with hyperopia), the parent will be advised to have the patient see the investigator as soon as possible. If the deviation is confirmed on examination, the decision as to whether to continue or discontinue therapy will be left to the

investigator and parent. If amblyopia treatment is to be discontinued prior to the primary outcome exam, the investigator's assigned Steering Committee member should be contacted to discuss the case and a masked examination arranged.

5.6. Risks of Examination Procedures

The procedures in this study are part of daily ophthalmologic 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.

5.7. Risk of Withholding Treatment in the Control Group

Standard care for a patient with amblyopia includes prescribing only spectacle correction initially and to continue this as long as the acuity in the amblyopic eye is improving. Thus, the maximum delay in treatment of the control group is 5 weeks. There is no known risk of withholding active treatment from the control group for 5 weeks. In the Amblyopia Treatment Study protocols conducted by our investigator group on patients in this age range, there has been no indication that the response to treatment is related to age; the response has been comparable in 6 year olds and 3 year olds. Thus, it is highly unlikely that a delay in initiating treatment of weeks or even months could be harmful.

5.8. Reporting of Adverse Events

1. Local side effects of treatment, worsening of visual acuity, and development of strabismus are to be noted on the Follow-up Examination Form.
2. Each investigator is responsible for informing his/her IRB of serious treatment-related adverse events and abiding by any other reporting requirements specific to his or her IRB.
3. Data on the complications of the study treatments will be tabulated regularly by the Coordinating Center for review by the Steering Committee. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

5.9. Intercurrent Events

1. If visual acuity should worsen in the amblyopic eye (or in the sound eye and does not recover with cessation or reversal of treatment), 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 dropped from the study. This will be reported on the Patient Final Status Form.
2. Eye injuries or the development of an eye problem that might affect vision will be reported on the Follow-up Examination Form. Likewise, the development of a serious medical problem that might affect the patient's study participation will be recorded.

CHAPTER 6: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

6.1. Sample Size Estimation For Randomized Trial

Although the primary analysis will include all patients with at least 3 lines inter-ocular difference at the time of randomization (regardless of their baseline amblyopic eye visual acuity), the sample size was estimated in order to have 90% power for a preplanned subgroup analysis of patients with baseline amblyopic eye acuity in the range of 20/40 to 20/100. Recruitment will continue until this quota is met. During the time period of recruitment, patients with acuity of 20/125 to 20/400 will be enrolled without a limit or formal sample size/power estimation. The number of enrolled patients with acuity of 20/125 to 20/400 is expected to be one-third of the number of patients with acuity of 20/40 to 20/100.

The sample size estimation was based on the standard deviation of the amblyopic eye visual acuity data from the 2-hour patching group in the ATS2B protocol (2-hours versus 6-hours patching for moderate amblyopia). The data were limited to those from patients with strabismic amblyopia because it is possible that some patients with anisometropic amblyopia experienced on-study acuity improvement that was related to optical correction. In strabismic patients in the ATS2B 2-hour group, the mean change in amblyopic eye acuity from baseline to 5-weeks was 1.7 logMAR. In the current study, we are expecting the amount of amblyopic eye improvement in the control group to be very small because (1) each patient will have had at least two visual acuity tests performed prior to randomization and most will have had more (minimizes the learning effect), (2) patients with refractive error will not be enrolled until acuity has been demonstrated to be stable on two acuity measurements, and (3) the time period between baseline and the outcome assessment is only 5 weeks (minimizes the age effect). However, because of the importance of detecting a beneficial treatment effect, assuming one exists, we have powered the study to be able to detect a mean difference between groups in amblyopic eye acuity of 0.10 logMAR.

With the assumptions of a standard deviation of 0.15 and a treatment group difference of 0.10 logMAR, we have selected a sample size of 100 (50 per group) to have 90% power for the subgroup analysis of patients with visual acuity 20/40 to 20/100. In estimating the sample size, we are ignoring the correlation between the baseline and 5-week acuities which when accounted for will increase power even further. If the correlation between the amblyopic eye baseline and 5-week acuities is on the order of 0.50, then the power is increased to approximately 99%. Also serving to increase the power of the primary analysis is the estimated 34 patients with visual acuity 20/125 – 20/400 that will be enrolled during recruitment of the 100 patients with visual acuity 20/40 – 20/100. Inclusion of these patients is expected to increase power to 96% (without adjusting for the correlation between acuities). These increases in power will offset any decreases in power from losses to follow up and withdrawals (which are expected to be few, in view of the short time period of the study) and treatment crossovers (control group patients receiving treatment or treatment group patients going off treatment)—also expected to be few in view of the short time period of the study).

6.2. Data Analysis Plan for Randomized Trial

The primary analysis will be a treatment group comparison of logMAR visual acuity scores obtained five weeks after randomization, adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model. As noted earlier, the primary analysis will include only those patients with at least 3 lines inter-ocular difference at the time of randomization. The primary analysis will follow the "intent-to-treat" principle. In the primary analysis, data will be included only from patients who complete the 5-week exam; there will be no imputation of data for patients who miss this exam.

No formal interim efficacy analyses of the outcome data are planned in view of the timing of its collection as it seems unlikely that there would be sufficient data and reason to terminate the trial early. However, a formal safety report will be provided to the DSMC twice a year.

The treatment effect in subgroups based on baseline factors will be assessed in preplanned secondary analyses. The subgroups of most interest will be those based on baseline amblyopic eye visual acuity (20/40 to 20/100 vs. 20/125 to 20/400), cause of amblyopia, and age.

A separate exploratory analysis will be conducted of data for patients with 2 lines inter-ocular difference at the time of randomization. This analysis will parallel the primary analysis.

6.3. Analyses of Spectacle Phase Data

Patients in the Spectacle Phase fall into one of the following two groupings:

1. Patients who meet only the anisometropia criteria described in section 2.2 (i.e., do not meet strabismus criteria) and who meet all the following:
   - No prior treatment for amblyopia
   - Spectacles not used in the 12 months prior to enrollment
2. Patients who require new spectacles, a change in spectacles, or who have been wearing the optimal spectacle correction for less than 16 weeks. This will include the following types of patients:
   - Cause of amblyopia is strabismus or combined mechanism
   - Cause of amblyopia is anisometropia only and spectacles are already being worn and/or patient previously treated for amblyopia.

The Spectacle Phase is skipped by patients who either do not need spectacle correction or who are already wearing the optimal spectacle correction for at least 16 weeks.

The primary objectives of the Spectacle Phase relate only to the patients who are enrolled with previously untreated anisometropic amblyopia (group #1 above). The analytic objectives include (1) to determine the time course of improvement with spectacles from onset of use to stabilization of acuity and (2) to determine the proportion of patients with previously untreated anisometropic amblyopia in whom the amblyopia resolves with spectacles alone.

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.

The Spectacle Phase of this study will allow us to estimate the resolution rate among anisometropic patients prescribed spectacles for the first time. For purposes of analysis, resolution will be defined as improvement of the amblyopic eye to be either within one line, the same, or better than the acuity in the sound eye.