AMBLYOPIA TREATMENT STUDY

ATS3

AN EVALUATION OF TREATMENT OF AMBLYOPIA IN 7 TO <18 YEAR OLDS

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PROTOCOL

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1 Objectives

- To determine the response rate of treatment of amblyopia in 7 to <13 year olds
- To determine the response rate of treatment of amblyopia in 13 to <18 year olds
- To determine the frequency of recurrence of amblyopia in 7 to <18 year olds after discontinuation of amblyopia treatment

1.2 Rationale for the Study

Most eye care practitioners believe that there is an age beyond which attempting to treat amblyopia is futile. Some believe that a treatment response is unlikely after age 6 or 7 years while others have an older age limit. There has not been a prospective clinical trial conducted with appropriate rigor that has evaluated the effect of treatment of amblyopia in children aged 7 years or older. Although available data on the efficacy of amblyopia treatment of older children are limited, there is reason to believe from clinical observations and published case series that treatment could have benefit. In a pilot study of patients 10 to <18 years old with amblyopia, we found that 37% of 52 patients showed improvement in the amblyopic eye acuity of 2 or more lines after treatment with part-time patching. However, without a concurrent randomized control group, the results are not conclusive. Although the literature and our pilot study provide support that amblyopia can be improved with treatment, neither the response rate to treatment nor the recidivism rate after cessation of treatment can be well defined. Despite the evidence that amblyopia therapy can be effective in older children, many clinicians do not attempt treatment under the assumption that it will be unsuccessful. Therefore, a clinical trial is needed to provide the requisite data to establish clinical practice guidelines for the treatment of amblyopia in older children. In addition to its importance for patient management, the trial's results will meet the demand for cost accountability by health maintenance organizations, large employers, and insurers.

1.3 Overview

1. The primary study design is a randomized trial comparing the visual acuity improvement in an Active Treatment Group (optical correction/atropine/patching) with the improvement occurring in a Control Group (optical correction only).
   - The randomized trial lasts from 6 weeks to 24 weeks for each subject

2. After completing the randomized trial:
   - Control Group patients will be offered treatment and followed outside of the study.
   - Active treatment patients whose acuity improves with treatment are observed for one year after treatment is discontinued to assess for a recurrence of amblyopia.

A synopsis of the study protocol follows.

I. Randomized Trial

A. Major Eligibility Criteria for Enrollment

- Age 7 to <18 years
- Amblyopia associated with strabismus, anisometropia, or both
- Visual acuity in the amblyopic eye 20/40 to 20/400 inclusive
- Visual acuity in the sound eye 20/25 or better

- No amblyopia treatment (other than spectacles) in the past month and no more than one month of amblyopia treatment in the last 6 months

B. Sample Size

A minimum of 90 patients in each of the age groups of 7 to <9, 9 to <11, 11 to <13, and 13 to <18 years old

C. Screening, Enrollment and Randomization

1. **Screening Examination** - a screening examination will be done to evaluate eligibility.
   - If optical correction is indicated, spectacles will be prescribed with the optimal refractive correction (paid for by the study; see section 2.5.2 concerning use of contact lenses).
     - The new spectacles will not be worn prior to the Randomization Examination.
2. **Randomization Examination** - the patient will return within 30 days for the Randomization Examination to measure visual acuity with the E-ETDRS protocol (with the new spectacles if prescribed).
   - Patients whose amblyopic eye acuity remains within the range of 20/40 to 20/400 inclusive and whose sound eye acuity remains 20/25 or better will be randomized to one of two treatment groups:
     - **Control Group** that receives optimal optical correction only
     - **Active Treatment Group** that receives optimal optical correction plus patching, near activities while patching, and atropine (not used in 13 to <18 year olds)
   - Patients whose amblyopic eye acuity no longer meets eligibility criteria will be discontinued from the study.

D. Visit Schedule and Testing

Patients are seen at 6-week intervals until criteria for either responder or nonresponder are met (see section 4.2) and are confirmed by masked exam.

- At each visit, visual acuity is measured in each eye and then acuity testing is repeated in the amblyopic eye.
  - Based on the better of the two amblyopic eye acuity scores, a determination is made at each visit as to whether the patient meets criteria for either *responder* or *nonresponder*.
    - *Responder* = improvement of 10 or more letters (2 lines) from baseline at either the 6, 12, 18, or 24 week visits
    - *Nonresponder* criteria are visit specific:
      6-week visit: 0 letter improvement from baseline (randomization) acuity

      12-week visit: 0 letter improvement from 6-week visit OR <3 letter improvement from baseline (randomization) acuity

      18-week visit: 0 letter improvement from 12-week visit OR <5 letter improvement from baseline (randomization) acuity

      24-week visit: <10 letter improvement from baseline (randomization) acuity

Participation in the randomized trial phase of the study ends when the *responder/nonresponder* classification is confirmed on a masked exam.

E. Primary Analysis

Comparison of *responder* rates in the Active Treatment Group and in the Control Group

II. Post-Randomized Trial Protocol

Control Group

Patients end formal study participation when criteria are met for *nonresponder*. They may then be started on active treatment and followed outside of the study.

Patients whose acuity improves 10 or more letters with spectacles alone (*i.e., meets responder criteria*) will continue follow up until there is no further improvement in acuity (as defined in section 4.5.1), at which time study participation will end and active treatment may be started (if acuity is still decreased) outside of the study.

Active Treatment Group

For patients meeting criteria for *nonresponder*, study participation ends at the conclusion of the randomized trial.

For patients meeting criteria for *responder,* treatment continues until there is no further improvement (as defined in section 4.5.2). When treatment is discontinued, these patients will enter an observation phase (see below).

C. Observation Phase

Active Treatment Group *responders* (patients who improved 10 or more letters [2 lines] on treatment) are continued in an observation phase for 12 months following the discontinuation of treatment.

Follow-up visits occur at 13, 26, and 52 weeks timed from the discontinuation of treatment.

If amblyopia recurs and meets the study's recurrence criteria, the investigator may re-institute any form of amblyopia therapy.

CHAPTER 2: SCREENING AND ENROLLMENT VISIT

2.1 Eligibility Assessment and Informed Consent

When a patient is found on a routine examination to be eligible for the study (see section 2.2), the study will be discussed with the patient and parent. Written informed consent will be obtained from the parent or guardian and the Child Assent Form will be signed by the patient.

Once a patient is randomized, that patient will be counted regardless of whether the assigned treatment is received or not. Thus, the investigator must not proceed to enroll a patient until he/she is convinced that the child and parent/guardian will accept either treatment group assignment.

2.2 Eligibility Criteria for Enrollment

Below are the eligibility criteria for enrollment. Note that visual acuity eligibility is reassessed at the Randomization Visit (see section 3.2.1). The visual acuity at the Randomization Visit is the baseline acuity for the randomized trial.

1. Age 7.0 to <18.0 years
2. 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: One or both of the following must be present:
     - ≥0.50 D difference between eyes in spherical equivalent
     - ≥1.50 D difference between eyes in astigmatism in any meridian
3. Visual acuity in the amblyopic eye 20/40 to 20/400 inclusive, using best correction based on the results of a cycloplegic refraction performed within past two months
   - Testing can be done with or without cycloplegia and using either the E-ETDRS testing protocol or the acuity testing procedure in routine office use.
     - If amblyopic eye visual acuity is borderline eligible (i.e., 20/40 or 20/400) using a routine office method of testing, retesting of the eye using the E-ETDRS testing protocol should be considered.
4. Visual acuity in the sound eye 20/25 or better using best correction based on the results of a cycloplegic refraction performed within past two months
5. No amblyopia treatment (other than spectacles) in the past month and no more than one month of amblyopia treatment in the last 6 months
6. No current active vision therapy or orthoptics
7. No ocular cause for reduced visual acuity on ocular examination performed within two months prior to enrollment
   - Nystagmus per se does not exclude the patient if the above visual acuity criteria are met
8. No myopia more than a spherical equivalent of -6.00 D in the amblyopic eye

9. No known allergy to bandage adhesives
10. No prior intraocular surgery
11. For patients <13 years old, no myopia (more than -0.50 D) in the sound eye
12. For patients <13 years old, no known reaction to or development of systemic side effects (e.g., confused mental state, somnolence, skin flushing, exacerbation of asthma) with prior use of atropine or other cycloplegics
13. For patients <13 years old, Down Syndrome not present
14. For patients <13 years old, patient will not be using a bifocal (if currently using a bifocal, it must be discontinued)
15. Parent willing to accept either treatment, available for at least 18 months of follow-up, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff

2.3 Historical Information

Historical information to be elicited will include: date of birth, gender, race, ethnicity, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, filters), refractive correction, and history of allergy/intolerance to bandage adhesive or atropine.

2.4 Screening/Enrollment Examination Procedures

The examination procedures are performed after the investigator has tentatively diagnosed amblyopia and has determined that the patient is likely eligible for the study.

1. Measurement of visual acuity in each eye <u>using best correction based on the results of a cycloplegic refraction performed within past two months</u>
   - Testing can be done <u>with or without cycloplegia</u>, using either the E-ETDRS testing protocol or the acuity testing procedure in routine office use *(although the E-ETDRS test is preferred, because this acuity test is for screening only and will not serve as the baseline acuity, routine office acuity testing can be done if more feasible)*.
     - If acuity is tested prior to cycloplegia and the cycloplegic refraction indicates a meaningful change from the refractive correction used to test the acuity, then the acuity should be retested after cycloplegia.
     - If the amblyopic eye acuity is borderline eligible (i.e., 20/40 or 20/400) using a routine office method of testing, retesting of the eye using the E-ETDRS testing protocol should be considered (*this may reduce the likelihood of enrolling a patient who will be ineligible at the randomization exam).*
2. Ocular examination as per the investigator's usual routine (if performed within two months prior to enrollment, does not need to be repeated)
3. Cycloplegic refraction (using cyclopentolate 1%) as per the investigator's usual routine (retinoscopy, subjective, or both)
   - The cycloplegic refraction does not need to be repeated if performed within the prior two months.
4. Eccentric fixation assessment of amblyopic eye assessed with or without dilation

2.5 Prescribing Spectacles/Contact Lenses

2.5.1 Spectacles

All enrolled patients will be prescribed a new pair of spectacles (with UV protection). If no refractive correction is needed (or if contact lenses are worn--see section 2.5.2), the patient will still be provided a pair of safety glasses.

In prescribing the optimal optical correction, hyperopia should be either fully corrected or undercorrected by no more than +1.50 D, anisometropia should be fully corrected, myopia should be fully corrected, and the full cylinder correction should be prescribed.

- *Because all patients will be prescribed a new pair of spectacles, there are no minimums for correction of refractive error.*

The patient 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 picked up by the patient on the day of the Randomization Visit. They should be carried to the office between pickup and the randomization visit. They should not be worn prior to the day of the Randomization Visit.

2.5.2 Contact Lenses

Although spectacles are the preferred method of optical correction for the study, contact lenses will be permissible in the circumstances listed below.

The study contact lens policy will be in keeping with conventional practice that reduced acuity in one eye is a relative contraindication to contact lens wear.

- If the patient is already wearing contact lenses in each eye, it will be recommended to the patient that he or she either discontinue the contact lenses or switch to wearing a single contact lens in the amblyopic eye (if this is feasible). If the patient persists with the desire to continue bilateral contact lens wear, the patient can still be enrolled and will be prescribed a pair of safety glasses to wear over the contact lenses.
- If the patient is not currently a contact lens user, then bilateral contact lenses cannot be prescribed as part of the study. The patient could be prescribed a single contact lens for the amblyopic eye, if feasible.

Contact lenses either can be fit in the investigator's office or the patient can be referred for contact lens fitting. The study will not pay for the fitting, supply, or replacement of contact lenses.

If contact lenses are being worn, after the lenses are fit, it will be necessary to verify that there is no significant residual refractive error by refracting over the contact lenses. If residual astigmatism >0.50 D or uncorrected anisometropia >0.50 D is present, either the contact lens prescription will be revised or spectacles will be prescribed to wear over the contact lenses.

For simplicity, in the remainder of the protocol, references to spectacles will also apply to contact lenses unless otherwise stated.

2.6 Enrollment of Eligible Patients

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

2.7 Scheduling Randomization Visit

The Randomization Visit will be within 30 days after the Enrollment Examination. It 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 randomization visit.

- Although it is preferable to complete the Randomization Visit at least one day after the Enrollment Visit, patients who either do not need refractive correction or do not need a change in refractive correction may complete both visits on the same day provided all testing can be completed according to the protocol-specified state of cycloplegia.

CHAPTER 3: RANDOMIZATION VISIT

3.1 Overview

The patient will return for the Randomization Examination within 30 days after the Enrollment Examination.

The visual acuity testing with any prescribed correction at the Randomization Examination is the baseline acuity for the randomized trial.

Prior to the visit, the office staff should verify that the spectacles (or contact lenses) prescribed at enrollment either have been received or that the patient will be picking them up on the day of the randomization visit.

- It is important that new contact lens wearers have adapted to wearing the lens in their amblyopic eye before the visual acuity testing is performed; therefore, visual acuity should not be measured until the contact lens wear is comfortable (testing must be completed within 24 hours of the time at which wear becomes comfortable--determination of this time is left to the investigator's discretion).

If the visual acuity testing demonstrates that the patient is eligible for randomization, the randomization procedure will be completed (see section 3.3). If the patient is no longer eligible, he or she will be discontinued from the study.

3.2 Measurement of Visual Acuity Prior to Randomization

If new spectacles were prescribed (and dispensed), they will be placed on the patient for at least 10 minutes prior to the testing.

- The spectacles prescription should be verified with a lensometer.

Visual acuity will be measured in each eye at distance using the E-ETDRS protocol (prior to cycloplegia, while the patient is wearing the prescribed optical correction) by an ATS-certified visual acuity tester. The testing procedure is detailed in the ATS Testing Procedures Manual.

- After a short break, acuity will be retested in the amblyopic eye.
- The baseline acuity in the amblyopic eye for the primary outcome will be considered to be the better score of the two tests.
  - If the acuity in either eye is worse than it was at enrollment and the patient was given new spectacles with an increase in the hyperopic correction, the possibility should be considered that the reduced acuity is due to latent hyperopia. If this is suspected, an overrefraction should be done with minus lenses to see if it improves the acuity. If the overrefraction improves the acuity, the baseline acuity test should be performed with the correction determined from the overrefraction.
  - If latent hyperopia is present and acuity in the sound eye is blurred, the patient will be asked to try to wear the spectacles at home with the expectation that he/she will relax into them. For patients whose acuity in the sound eye remains blurred for more than one week, the spectacle correction can be changed by reducing the plus the smallest amount necessary to optimize acuity.
- The patient will be randomized as long as the amblyopic eye acuity (better score on the two tests) is 20/40 to 20/400 inclusive (letter score 20 to 70 inclusive) and the sound eye acuity is 20/25 or better (letter score $\geq$80).

- If the acuity in the amblyopic eye is better than 20/40 or worse than 20/400, the patient will not be randomized and will be discontinued from the study. *Such patients are expected to be very few. They will still be given a Game Boy to avoid the possibility that a patient might volitionally test poorer than true acuity in order to be randomized into the study and get a Game Boy.*
- If acuity in the sound eye is worse than 20/25, it can be retested with the same or a different refractive correction (see above).

3.3 Additional Examination Procedures

After visual acuity testing, the following examination procedures can be performed either before or after randomization. Testing should be performed in the following order:

1. Binocularity testing: Titmus Fly, Randot Preschool Test, and Worth 4-dot Test (the testing procedures are described in the ATS Testing Procedures Manual and on the exam form)
2. Measurement of predominant alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near (the testing procedure is described in the ATS Testing Procedures Manual) and assessment of the presence of primary position nystagmus (with and without monocular occlusion)
    - If acuity is too poor to fixate for SPCT, a modified Krimsky test should be performed (the testing procedure is described in the ATS Testing Procedures Manual).
3. For patients 7 to <13 years old, assessment of reading ability 25-40 minutes after cycloplegia of sound eye (the testing procedure is described in the ATS Testing Procedures Manual)
    - This assessment can either be made prior to randomization in both treatment groups or after randomization in just those patients assigned to the Active Treatment group.
    - The assessment should be made while the patient is wearing optical correction.
    - For patients who are unable to read grade-appropriate print, reading glasses will be prescribed. The power of the reading glasses can either be prescribed as +2.50 greater than the distance optical correction for each eye or at investigator discretion (see section 4.2.3).

3.4 Steps to Complete Randomization

Assuming that visual acuity in the amblyopic eye on the better of the initial and repeat tests is 20/40 to 20/400 inclusive and acuity in the sound eye is 20/25 or better, the patient will be randomly assigned with equal probability to either (1) the Active Treatment Group or (2) the Control Group.

The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by site, which will specify the order of treatment group assignments. A patient is officially randomized when the randomization process detailed below is completed.

The patient's treatment group assignment can be obtained either by entering the Randomization Examination Form on the ATS website or by faxing the form to the Jaeb Center. A Randomization Report listing the patient's initials, identification number, treatment group, and visit schedule will be printed from the web or faxed to the site along with a patient treatment instruction sheet and patient home calendar logs to record the treatment and near activities.

3.5 Miscellaneous Considerations

Enrolled patients who miss the Randomization Visit will be contacted and an attempt will be made to reschedule. Patients who do not have the Randomization Visit within two months of the Enrollment Examination will be dropped from the study

CHAPTER 4: PROTOCOL FOR THE RANDOMIZED TRIAL

4.1 Overview

The study design is a randomized trial comparing the visual acuity improvement in a treatment group with the improvement occurring in a control group. The randomized trial lasts from 6 weeks to 24 weeks for each subject.

- The Control Group is prescribed no treatment other than optical correction
  - Patients end formal study participation when criteria are met for *nonresponder* (see next section). They will then be offered active treatment and followed outside of the study.
  - Patients whose acuity improves 10 or more letters with spectacles alone (*i.e., meets responder criteria—see next section*) will continue follow up until there is no further improvement in acuity (as defined in section 4.5.1) at which time study participation will end and active treatment will be started (if acuity is still decreased) outside of the study.
- The Active Treatment Group is prescribed optical correction plus 2 to 6 hours per day of patching and near visual tasks for at least one hour a day while wearing the patch. Patients 7 to <13 years old are also prescribed daily atropine *(it was felt that the potential greater impact on older teenage activities, such as driving, precluded the use of atropine in the older group).*
  - For patients meeting criteria for *nonresponder* (see next section), study participation ends at the conclusion of the randomized trial.
  - For patients meeting criteria for *responder* (see next section), treatment continues until there is no further improvement (as defined in section 4.5.2). When treatment is discontinued, these patients will enter an observation phase (see below).

Patients are seen at 6-week intervals (within a time window of ±1 week) until criteria for either responder or nonresponder are met (see next section) and are confirmed by masked exam.

- At each visit, visual acuity is measured in each eye and then acuity testing is repeated in the amblyopic eye.
  - Based on the better of the two amblyopic eye acuity scores, a determination is made at each visit as to whether the patient meets criteria for either *responder* or *nonresponder* (see next section).

4.2 Definitions of *Responder* and *Nonresponder*

Responder: ≥10 letter (2 line) improvement in the amblyopic eye acuity compared with the baseline acuity at any one of the 6, 12, 18, or 24 week visits timed from randomization.

Nonresponder: criteria are visit specific:

- **6-week visit:** 0 letter improvement from baseline (randomization) acuity
- **12-week visit:** 0 letter improvement from 6-week visit OR <3 letter improvement from baseline acuity
- **18-week visit:** 0 letter improvement from 12-week visit OR <5 letter improvement from baseline acuity
- **24-week visit:** <10 letter improvement from baseline acuity

An alternative way to interpret the *nonresponder* criteria at each visit is given below:

Visit	If answer below is NO, the patient meets *nonresponder* criteria
6 wks	Acuity improved at least 1 letter from baseline?
12 wks	Acuity improved at least 1 letter from 6-wk visit and at least 3 letters from baseline?
18 wks	Acuity improved at least 1 letter from 12-wk visit and at least 5 letters from baseline?
24 wks	Acuity improved at least 10 letters from baseline?

If a patient misses a 6 week or 12 week visit, the visual acuity from the last completed protocol-specified visit will substitute for the missed visit acuity in determining whether the *nonresponder* criteria are met at the next visit (e.g. at the 18 week visit, the *nonresponder* criteria for a patient who missed the 12 week visit will be 0 letters of improvement from the 6 week visit or <5 letter improvement from baseline acuity).

4.3 Treatment Regimens

4.3.1 Control Group

The control group is given no treatment other than wearing the optimal optical correction (if indicated).

- If non-protocol active treatment for amblyopia is received (i.e., the patient receives treatment such as atropine or patching to impair the vision in the sound eye), the patient will be classified as a *nonresponder*.
- When study participation ends (either at the time that *nonresponder* criteria are met or if *responder* criteria are met, when there is no further improvement (as defined in section 4.5.1), the patient will be offered treatment and followed off study (the study will provide a Game Boy and will supply patches and atropine if prescribed for the patient even though treatment is being completed off study).

4.3.2 Active Treatment Group

The treatment regimen is the same for the patients 7 to <13 years old and for patients 13 to <18 years old, except that the older age group will not be using atropine.

The treatment regimen will include all of the following:

1. Atropine 1% one drop once a day (in the morning preferred) in the sound eye (7 to <13 year olds only)
2. Patching of the sound eye after school and on weekends for a minimum of 2 hours daily and a maximum of 6 hours daily
3. Near visual tasks while wearing the patch for at least one hour per day
   - The investigator may use his/her discretion with regard to which specific visual activities to prescribe based on what he/she believes are suitable for the child's age and may be beneficial. These tasks may include:
     - Crafts, coloring, tracing, cutting out objects, dot-to-dot connecting, 'fill in the symbols,' 'symbol sequence,' or other activities requiring eye-hand coordination
     - Hidden pictures and word finds
     - Video games (e.g., Game Boy/Nintendo)
       - A Game Boy will be provided by the study
     - Computer/internet

- Written homework
- Reading
- Home Activities Workbook provided by the investigator
- Other accommodative tasks

This treatment regimen is maintained until the patient has met the criteria for an outcome classification as either a *responder* or *nonresponder* (see section 4.2). The only exception is that modification of the atropine regimen (applies only to patients <13 years old) will be permitted if the atropine is not tolerated.

- Patients who meet the *nonresponder* criteria discontinue study participation.
- Patients who meet the *responder* criteria remain on treatment as long as there is continued improvement (as defined in section 4.5.2) in acuity. However, the investigator may alter the prescribed treatment regimen including adding new treatment modalities (see section 4.5.2).

4.3.2.1 Treatment Considerations

1. Treatment should begin on the day of or the day following randomization.
2. The study will provide patches and atropine. Patients using atropine will be advised to wear spectacles or sunglasses with UV protection and a brimmed hat when outdoors.
3. Active Treatment Group patients will be given a patient home calendar log to record the treatment received and will be asked to bring the completed calendars to each visit.
4. Patients prescribed atropine who (1) are unable to read the grade-appropriate print at the randomization visit with the sound eye cyclopleged and (2) will be attending school while on treatment will be prescribed single vision reading glasses to use during school (paid for by the study). *Note: single vision reading glasses are being prescribed rather than bifocals to avoid the problem of the bifocals being worn all of the time, thus potentially compromising the effect of the atropine.*
   - The power of the reading glasses can either be prescribed as +2.50 greater than the distance optical correction for each eye or at investigator discretion.
   - If reading glasses are not prescribed at randomization but the patient later has difficulty in school due to the reduced acuity in the sound eye, reading glasses will be prescribed at that time.

4.4 Follow-up Visit Schedule and Testing

During the randomized trial phase of the study, protocol-specified visits occur every six weeks (±1 week) for up to 24 weeks, as long as the amblyopic eye acuity has improved since the last visit and the patient does not meet criteria for *nonresponder* (see section 4.2). Additional visits are at the discretion of the investigator.

At each follow-up visit, visual acuity is measured with the E-ETDRS protocol by an ATS-certified visual acuity tester in the right eye, then in the left eye, then repeated in the amblyopic eye

- The amblyopic eye will be tested without cycloplegia with the optical correction being worn at home. If a refraction is done and it denotes a change, the repeat testing can be done using best correction obtained using trial frames or a phoropter.
- The sound eye can be tested with the optical correction worn at home, trial frames, or a phoropter, using whichever method the investigator believes is necessary to obtain the best acuity. For patients using atropine, it may be necessary to use trial frames or a phoropter if

the spectacles (or contact lenses) do not contain the full hyperopic correction in order to obtain the best sound eye acuity.

At the 6 week follow-up visit only, the Worth 4-dot test will also be completed.

4.4.1 Masked Visual Acuity Testing

When the acuity testing at the 6, 12, 18, or 24 week follow-up visit indicates that a patient has met criteria for *responder* or *nonresponder*, a masked exam is arranged to verify the outcome classification.

The masked examiner will not know either the treatment group or the acuity score from the unmasked visual acuity test (i.e., the examiner will not know whether the patient met the *responder* or *nonresponder* criteria).

In order to maintain treatment group masking, for patients 7 to <13 years old, a patch must be placed over the sound eye of the patient before the masked examiner sees the patient (because of pupil dilation from atropine).

Masked visual acuity testing can be done at the same office visit if a certified visual acuity tester who does not know the patient's treatment group is available, otherwise, the patient will be scheduled to return for the masked exam within two weeks.

If a masked exam has not been done prior to the 24-week visit, it will be performed at that visit.

If the masked examination does not verify the classification of the patient as a *responder* or *nonresponder*, then the patient will continue in follow up (if the masked exam was performed at a visit prior to 24 weeks) and the masked exam will be repeated when indicated at a subsequent visit.

4.5 Continuation of Follow Up for Patients Meeting Criteria for *Responder*

4.5.1 Control Group

Patients who improve 10 or more letters with optical correction alone will continue to be followed at six week intervals until no further improvement (an increase in visual acuity of less than 3 letters from the prior visit) occurs with optical correction alone. At that time, study participation ends and at investigator discretion, the patient can be started on treatment and followed off study.

4.5.2 Active Treatment Group

For patients meeting criteria for *responder* in the randomized trial (10 or more letters [2 lines] improvement from baseline), treatment and follow up continue every six weeks until there is no further improvement, defined as described below.

- Once the responder criteria are met, the treatment protocol used in the randomized trial can be continued or modified and any other treatment modality can be prescribed, including atropine for patients 13 to <18 years old or in-office vision therapy.
- The decisions as to whether to taper treatment and when to discontinue treatment are also at investigator discretion, subject to the following stipulation:
  - If treatment continues past 24 weeks, it must continue for no more than 6 weeks beyond the visit at which improvement in the prior 6-week period has been <3 letters.
    - If the patient returns for another visit and the acuity indicates an improvement of 3 or more letters, treatment may be continued.

Once treatment is discontinued, follow up continues in the observation phase (see chapter 5).

CHAPTER 5: OBSERVATION FOR RECURRENCE

5.1 Overview

To determine the rate of recidivism following successful treatment, after treatment is discontinued, Active Treatment Group responders (patients who improved 10 or more letters [2 lines] on treatment) in the randomized trial are continued in an observation phase for 12 months.

5.2 Visit Schedule

Follow-up visits will occur at 13, 26, and 52 weeks timed from the discontinuation of treatment. Additional visits are at the discretion of the investigator.

5.3 Examination Procedures

At each visit, distance visual acuity will be measured in each eye without cycloplegia and with appropriate refractive correction by the E-ETDRS testing protocol. There is no masked testing of visual acuity in the observation phase.

A refraction should be done at least once during the observation phase of the study.

At the 13-week and 52-week observation phase visits, the following additional testing will be done:

- Measurement of ocular deviation in primary position at distance and near by Simultaneous Prism and Cover Test (SPCT). If visual acuity is too poor to fixate for SPCT, a modified Krimsky test should be performed as described in section 3.2.
- Binocularity testing (Titmus Fly and Randot Preschool Test)

5.4 Recurrences of Amblyopia

5.4.1 Definition of Recurrence

A recurrence of amblyopia is defined as two consecutive visual acuity measurements in the amblyopic eye that are 10 or more letters worse than the acuity at the time treatment was discontinued. The two measurements can be made on the same day or on different days.

- Recurrence may be declared at any visit (protocol-specific or additional visit). If at the 52-week observation phase visit, a patient who has not previously been classified as having a recurrence has a decrease in visual acuity of 10 or more letters (as described above) on a single measurement and the measurement is not repeated on that day, a repeat acuity testing on a subsequent day will be considered to be part of this visit.
- If a refraction has not been performed within the prior six months, as per usual clinical practice it should be repeated before retesting acuity and classifying a patient as having a recurrence.

5.4.2 Treatment of Amblyopia Recurrence

If amblyopia recurs and meets the study's recurrence criteria, the investigator may institute any form of amblyopia therapy, which will be recorded on the follow-up exam form. If an investigator believes that treatment should be reinstituted but the patient has not met the study's recurrence criteria, a Protocol Chair should be contacted to discuss the case.

Patient follow up will continue through the close-out visit, with collection of treatment and acuity data.

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

6.1 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 patient and family and, where needed, to help coordinate scheduling of examinations.

- One phone contact is planned for each patient in the first month after enrollment and in the first month after entry into the observation phase. Additional phone contacts will be made if necessary to facilitate patient scheduling for follow-up visits.

6.2 Patient Withdrawals

A patient (and in this case the parents or guardian) may withdraw from the trial at any time. 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, every effort should be made to comply with this and to attempt to keep the patient in the study under the new provider's care.

6.3 Management of Optical Correction

A refraction can be performed at any time the investigator suspects that refractive error may not be optimally corrected.

6.4 Management of Strabismus

Strabismus surgery, vision therapy for strabismus, orthoptics, and prisms are allowed at the discretion of the clinician. These will be recorded in the comment section of the Follow-up Examination Form.

6.5 Adverse Events/Risks

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

6.5.1 Side Effects of Atropine

1. Local side effects of minimal severity include allergic lid reactions, local irritation, conjunctival hyperemia, and follicular conjunctivitis. Potential systemic side effects include dry skin and mouth, tachycardia, fever, flushing irritability, mental confusion, constipation, aggravation of asthma, and seizures. Systemic effects occur very uncommonly in the dosage schedule (one drop a day) suggested in this protocol as noted in the previous studies of atropine treatment. Simons and coworkers[1] found the risk of allergic reactions to be less than 1%. Additional safety data can be derived from the literature describing the chronic topical atropine treatment for the attempted prevention of myopia. In the study by Brodstein and colleagues,[2] 253 patients were treated for an average of 33 months with daily atropine 1% drops. Neither local nor systemic side effects of any significance were noted. In ATS1,[3] among 204 patients, an ocular side effect was reported at least once for 26% of patients, most commonly light sensitivity (18%), lid or conjunctival irritation (4%), and eye pain or headache (2%). Parents were queried about the occurrence of a systemic side effect at each follow-up visit during atropine treatment. Facial flushing was reported for two patients, one of whom remained on atropine with no further problems and one of whom was switched to homatropine. Atropine was not discontinued because of side effects in any other patients. No other systemic side effects of atropine were reported.

2. Atropine produces dilation of the pupil, which can increase the light that enters the eye. Although it has not been demonstrated that atropine used for a several month duration will have harmful ocular effects, excessive exposure to light theoretically could be toxic to the retina. Atropine has been used long-term to prevent the progression of myopia without an apparent adverse effect on acuity.[2, 4-6]

   To minimize risks, the following steps will be taken:
   - Investigators will review the identification and management of atropine toxicity at the prestudy meeting/conference calls.
   - Atropine will be dispensed in child-proof containers and parents will be instructed to keep the atropine away from children.
   - To minimize risk from pupil dilation, sunglasses with UV protection (or flip-ups, for patients who require glasses) will be provided and the wearing of a brimmed hat will be encouraged.

3. When a patient develops adverse effects serious enough to discontinue atropine, the investigator should call a Protocol Chair to discuss the protocol to follow. If atropine is discontinued, then the patient can be switched to homatropine 5% once a day. Such a change in the treatment regimen will be recorded on a follow-up examination form. Homatropine, if needed, will be sent directly to the patient from the Jaeb Center.

6.5.2 Side Effects of Patching

Patching could cause mild skin irritation. However, in view of the small number of hours of daily patching prescribed in the study, substantial skin irritation is highly unlikely.

6.5.3 Reverse Amblyopia

The study treatment for amblyopia could decrease the visual acuity in the sound eye, although this is almost always reversible and is rare in the age group included in this study.

The diagnosis and management of reverse amblyopia is left to the investigator's judgment.

If reverse amblyopia is suspected, a suggested routine for evaluation is the following:

1. If not already done, recheck acuity using full hyperopic correction from the most recent cycloplegic refraction.
2. If acuity is still decreased, perform a refraction and recheck acuity if testing was not done with proper hyperopic correction.
3. If acuity is still worse, stop therapy and repeat visual acuity testing in one week.
4. If the visual acuity has returned to enrollment level, resume treatment as per protocol.
5. If still reduced after one week, contact a Protocol Chair to discuss the case and further treatment.

6.5.4 Diplopia

Amblyopia therapy could induce diplopia through occlusion of the dominant eye and disruption of habitual suppression of the non-dominant eye during binocular conditions. Although rare, it is possible that the diplopia could persist even after treatment is discontinued. Data on the frequency of this complication will be collected as part of the ATS3 study.

6.5.5 Risks of Examination Procedures

The procedures in this study are part of daily ophthalmologic and optometric practice in the United States and pose no additional known risks. Dilating/cycloplegic eye drops may normally be used as part of an exam.

6.5.6 Reporting of Adverse Events

Occurrence of an adverse event such as side effects of treatment, worsening of visual acuity, and development of strabismus is to be indicated on the Follow-up Examination Form and will be described in detail on the Adverse Event Form. In addition, the following serious complications must be reported to the Jaeb Center within 24 hours as a narrative by FAX or e-mail.

- Patient death
- Angle-closure glaucoma
- Any serious suspected systemic atropine toxicity

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/her IRB.

Adverse effects of treatment are recorded on each follow-up exam form. These data will be tabulated regularly by the Data Coordinating Center. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee (DSMC), which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to the investigators to submit to their IRBs.

6.6 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 (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 Follow-up Examination Form.

2. If treatment precipitates the development of an ocular deviation (e.g., esotropia in a patient 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's decision.

3. 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 7: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The sample size estimation and analysis plan are summarized herein and will be detailed in a separate document.

7.1 Sample Size

The approach to estimation of sample size is in concert with the analysis plan in which *responder* proportions will be compared between the Control Group and the Active Treatment Group. The age group of 7 to <13 years olds will be analyzed separately from the age group 13 to <18 years old. Within the 7 to <13 year olds, stratum-specific analyses will be conducted for the age groups of 7 to <9, 9 to <11, and 11 to <13 years. Thus, the sample size was computed separately for each stratum.

7.1.1 Projected *Responder* Rates

The *responder* rate for the Control Group is estimated to be 5% throughout the age range of 7 to <18 years old.

The literature and our pilot study support a *responder* rate of 50% or more for the Active Treatment Group for ages through <18 years old. However, because retrospective data often overestimates outcome rates, we have decided to project more conservative *responder* rates as follows: age 7 to <9: 50%, 9 to <11: 35%, 11 to <13: 25%, 13 to <18: 25%.

7.1.2 Sample Size Selection for Various Success Proportions

Table 7.1 reports **total** sample sizes for various treatment effects based on a two-group Fisher's exact test.

Table 7.1: Total Sample Size Estimates for a Range of Treatment Group *Responder* Rates*

Responder Proportion		Power	
Active Treatment Group	**Control Group**	**80%**	**90%**
.15	**.05**	252	330
.25	**.05**	**90**	114
.35	**.05**	50	66
.50	**.05**	28	36

*one-sided alpha = .05

In selecting a sample size, we have decided to have a minimum of 80% power for the range of projected *responder* rates in the Active Treatment Group. We have selected a one-sided alpha because we are only interested in whether the Active Treatment Group is better than the control group and not vice versa. With 80% power and a one-sided alpha of .05, the minimum total sample size for a stratum is computed to be 90 patients. Because patients who withdraw or are lost to follow-up will be considered nonresponders, the sample size has not been increased to account for incomplete follow-up.

Assuming that the control group *responder* rate of .05 is not an underestimate, power will be 90% or greater for strata with a *responder* rate of at least .30.

It is anticipated that recruitment will be continued in 7 to <13 year olds until the stratum with the slowest recruitment rate reaches 90, with recruitment continuing beyond 90 in the other strata.

7.2 Primary Analyses

The primary analysis will be a comparison of *responder* proportions in the randomized trial with a Fisher's exact test (StatXact software; Cytel, Inc.).

To be classified as a treatment *responder* for the primary analysis, a patient must have at least a 10 letter improvement from baseline in the amblyopic eye visual acuity at any one of the 6, 12, 18, or 24 week visits timed from randomization. Patients not meeting these criteria will be considered *nonresponders,* including patients with incomplete follow-up.

In 7 to <13 year olds, the *responder* proportions between treatment groups will be compared separately in the three age strata of 7 to <9, 9 to <11, and 11 to <13 years old. In 13 to <17 year olds, the primary analysis will be for the full age range.

Among the treatment *responders*, the magnitude of improvement in visual acuity in the amblyopic eye will be tabulated according to both the number of lines of improvement from visual acuity at randomization and the final level of visual acuity.

Other analyses will evaluate the relationship between age and the magnitude of the treatment effect. Subgroup analyses will explore differences in treatment effect with moderate and severe amblyopia and according to cause of amblyopia.

CHAPTER 8: REFERENCES

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