AMBLYOPIA TREATMENT STUDY

ATS2

AN EVALUATION OF PATCHING REGIMENS FOR AMBLYOPIA

A. A Randomized Trial Comparing Part-time Versus Full-time Patching for Severe Amblyopia

B. A Randomized Trial Comparing Part-time Versus Minimal-time Patching for Moderate Amblyopia

C. An Observational Study on Recurrence of Amblyopia After Discontinuation of Treatment

PROTOCOL

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ATS2 CONTACT INFORMATION

Jaeb Center for Health Research
3010 East 138th Avenue, Suite 9
Tampa, FL 33613
Phone (888) 79PEDIG or (813) 975-8690
Fax (888) 69PEDIG or (813) 975-8761

Jaeb Center

Roy W. Beck, M.D., Ph.D.
Home: (813) 933-7907; (813) 932-9174
Cell: (813) 690-9411
rbeck@jaeb.org

Heidi A. Gillespie
Home: (813) 985-5552
Cell: (813) 690-9419
hgillespie@jaeb.org

Pamela S. Moke, M.S.P.H.
Home: (813) 975-0529
Cell: (813) 690-9418
pmoke@jaeb.org

Raymond Kraker
Home: (813) 814-1136
Cell: (813) 690-9415
rkraker@jaeb.org

Nicki Boyle
nboyle@jaeb.org
Cell: (813) 690-9414

ATS2 Chairmen

Michael X. Repka, M.D.
Business: (410) 955-8314
Home: (410) 532-0280
Pager: (410) 283-2771
Cell: (410) 227-9748
mrepka@jhmi.edu

Jonathan M. Holmes, M.D.
Business: (507) 284-3760
Home: (507) 281-1208
Pager: (507) 284-2511
(ask for Dr. Jonathan Holmes of Ophthalmology)
holmes.jonathan@mayo.edu

CHAPTER 1
BACKGROUND AND SUMMARY

1.1 Overview

ATS2 will consist of two concurrent randomized trials for patients with amblyopia in the range of 20/40 to 20/400 and one observational study. Investigators can participate in all or any of the three.

A. A randomized trial comparing part-time (6 hours) and full-time (all or all but one waking hour) of daily patching for 4 months for severe amblyopia (20/100 to 20/400)

B. A randomized trial comparing part-time (6 hours) and minimal time (2 hours) daily patching for 4 months as treatment for moderate amblyopia (20/40 to 20/80)

C. A prospective observational study to determine the amblyopia recurrence rate and factors associated with recurrence when treatment is discontinued in patients whose amblyopia has been successfully treated.

1.2 Rationale for the Study

Amblyopia is the most common cause of monocular visual impairment in both children and young and middle-aged adults. Patching has been the mainstay of amblyopia therapy. It is generally held that the response to treatment is best when it is instituted at an early age, particularly by age two or three, and is poor when attempted after eight years of age.

For severe amblyopia, it is generally accepted that occlusion with patching is the standard of care. Other modalities of treatment, such as atropine penalization and optical penalization, are widely considered insufficient as initial treatments for severe amblyopia. However, controversy exists with regard to how many hours per day of patching should be prescribed. Advocates of *full-time* patching purport that such a regimen is needed to restore visual acuity more rapidly and more effectively. Advocates of *part-time* patching believe it to be better tolerated by the child and family, therefore producing less stress on the parent-child relationship and producing better results through better compliance. *Part-time* patching may also promote the development of binocularity in patients who have "straight-eyes", reduce the chance of a straight-eyed patient developing manifest strabismus or losing stereopsis, and reduce the incidence of reverse- or occlusion-amblyopia.

For moderate amblyopia, patching is the most commonly prescribed treatment although other modalities such as atropine penalization are also prescribed. ATS1 is comparing patching and atropine therapies for moderate amblyopia. There is no specific patching regimen that is widely accepted for treatment of moderate amblyopia and limited or no data available to favor the use of one specific regimen; both minimal occlusion (e.g., 2 hours per day) and six or more hours per day of patching are prescribed in clinical practice. Even if ATS1 demonstrates that atropine is as effective a treatment as patching for moderate amblyopia, there will still be a need to evaluate minimal-duration patching as an alternative to longer-duration patching and atropine.

After amblyopia has been successfully treated, there is no accepted standard of care for how it should be managed. Can treatment be stopped or is a period of maintenance therapy needed? At present, there are little quality data available on the recurrence rate of amblyopia and whether there are any factors that can predict which patients are likely to have a recurrence and which are not. Therefore, a prospective data collection is warranted to provide an estimate of the

amblyopia recurrence rate and associated factors. This may lead to a later randomized trial comparing treatment cessation versus a period of maintenance therapy.

1.3 Synopsis of Study Design for the Randomized Trials

Major Eligibility Criteria

The eligibility criteria for the two randomized trials are the same with the exception that the amblyopic eye visual acuity for study A is 20/100 to 20/400 and for study B is 20/40 to 20/80 and the stipulation that patients in study A not be within 4 months of entering first grade.

- Age < 7 years
- For study A, not in or within 4 months of entering first grade
- Able to measure surrounded single optotype visual acuity using the ATS protocol *(this will in effect exclude all patients <2 years old and many <3 years old)*
- Amblyopia associated with strabismus, refractive error/anisometropia, or both
- Visual acuity in the amblyopic eye ≤ 20/40 and ≥20/400 (study A: 20/100-20/400 and study B: 20/40-20/80)
- Visual acuity in the sound eye ≥ 20/40 and inter-eye acuity difference ≥3 logMAR lines
- No prior amblyopia therapy or if there has been prior therapy, it must meet the following criteria: (1) no patching treatment within 6 months prior to enrollment, and (2) no other amblyopia treatment of any type (other than spectacles) used within one month prior to enrollment. Any treatment more than 6 months prior to enrollment is acceptable.

Treatment Groups

All treatment regimens are for 4 months unless the acuity in the amblyopic eye improves to be no more than one line worse than the sound eye or reverse amblyopia develops (see section 2.2.2.1).

Study A (severe amblyopia) 20/100 to 20/400

- Part-time patching: 6 hours per day
- Full-time patching: all or all but one hour of patching per day

Study B (moderate amblyopia) 20/40 to 20/80

- Part-time patching: 6 hours per day
- Minimal-time patching: 2 hours per day

Sample Size

Study A and Study B will each enroll approximately 160 patients assigned equally to the treatment groups.

Visit Schedule and Outcome

- Minimum of 2 visits at 5 weeks and 17 weeks (additional visits at investigator discretion)
- Primary outcome: visual acuity at 17-week visit

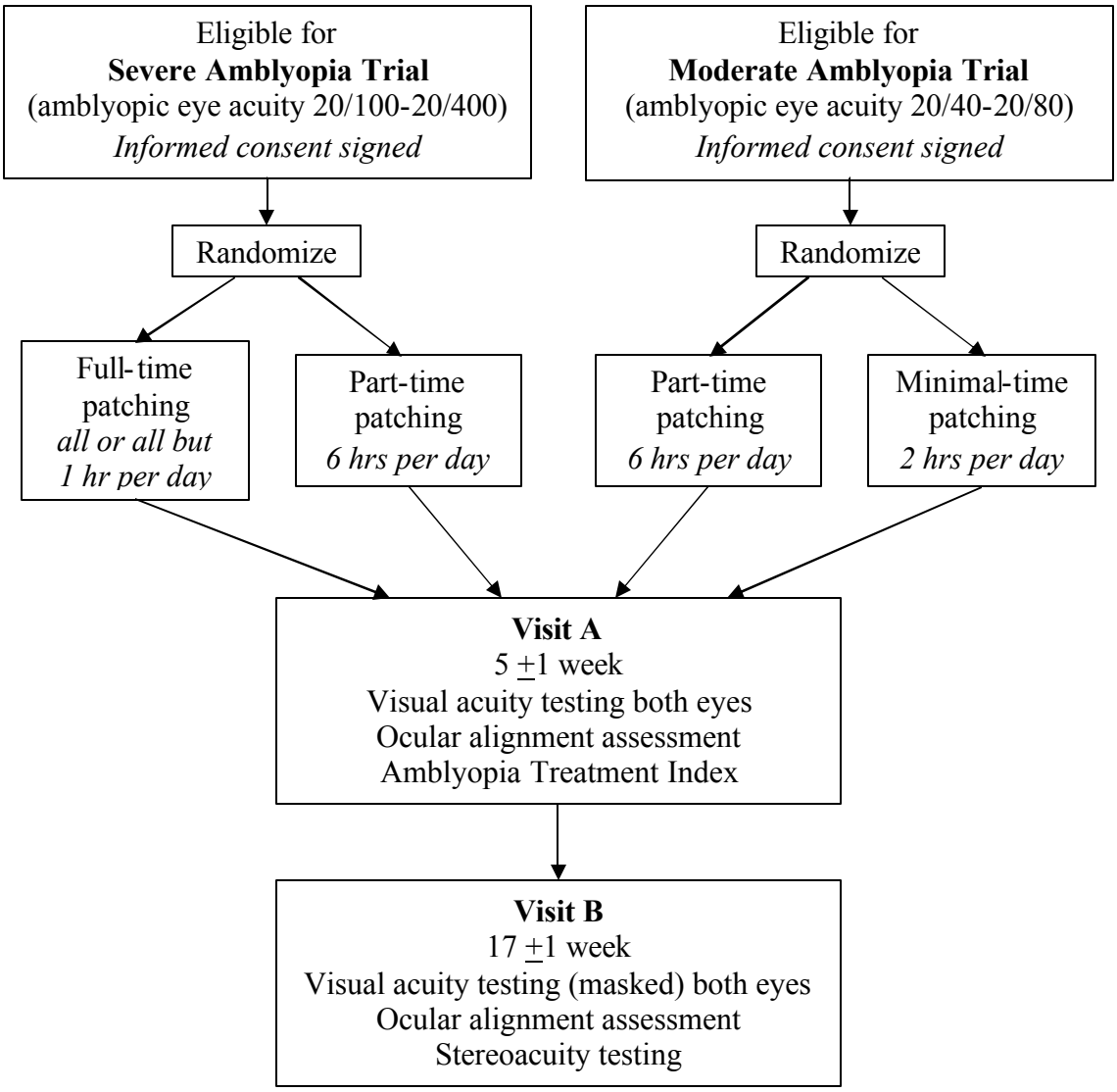
Primary Analysis

The primary analytic approach in each trial will involve treatment group comparisons of logMAR visual acuity scores obtained four months after randomization, adjusted for baseline visual acuity scores in analysis of covariance (ANCOVA) models.

ATS2 Randomized Trials Flow Chart

MAJOR ELIGIBILITY CRITERIA

- Age < 7 years
- Able to measure surrounded single optotype visual acuity using the ATS protocol
  (this will in effect exclude all patients <2 years old and many <3 years old)
- Amblyopia associated with strabismus, refractive error/anisometropia, or both
- Visual acuity in the amblyopic eye ≤ 20/40 and ≥20/400
- Visual acuity in the sound eye ≥ 20/40 and ≥3 logMAR line inter-eye difference
- No prior amblyopia treatment; or if prior therapy, it must meet specific study criteria.



1.4 Synopsis of Study Design for Amblyopia Recurrence Observational Study

The purpose of this study is to collect data to estimate the recurrence rate of amblyopia after treatment is discontinued and to identify factors associated with recurrence to be considered in designing a subsequent randomized trial. Statistical analyses primarily will be exploratory.

Major Eligibility Criteria

The study will enroll both patients who participated in one of the ATS randomized trials and other patients. Patients in ATS1 can be enrolled after their primary outcome visit at 6 months. Patients in ATS2 cannot be enrolled until their follow-up has ended at 4 months.

- Age <8 years
- Continuous treatment for amblyopia in the last 3 months that has been at least 2 hours/day of patching (14 hours per week) or at least one drop of atropine per week (within one week of enrollment)
- Ready for cessation of treatment in investigator's judgment
- Original cause of amblyopia – strabismic, anisometropic, or combined; prior to treatment acuity in amblyopic eye 20/40 or worse with at least 3 logMAR lines interocular acuity difference.
- If patient has been in ATS1 or ATS2 randomized trial, visual acuity in amblyopic eye at the time of enrollment into the Observational Study has improved by at least 3 logMAR lines from the ATS baseline acuity (measured using the ATS visual acuity testing protocol)
- If patient was not in ATS1 or ATS2 randomized trial, acuity in amblyopic eye at the time of enrollment into the Observational Study has improved by the equivalent of at least 3 logMAR lines from the pretreatment level (measured using the same acuity measurement technique at both time points) and is at least 20/80 by ATS acuity protocol on the PC Vision Tester

Sample Size

Recruitment will continue until 100 patients with "immediate cessation" of treatment have been recruited (patching or atropine at maximal intensity within one week of enrollment or at least "half-maximal" intensity within one week of enrollment, with no previous reduction to less than half-maximal).

Patient Management

Amblyopia therapy discontinued

Visit Schedule

- Minimum of 4 visits at 5 $\pm$ 1 week, 13 $\pm$ 2 weeks, 26 $\pm$ 2 weeks, and 52 $\pm$ 2 weeks (additional visits at investigator discretion)

Primary Outcome

Recurrence of amblyopia within 12 months of discontinuation of amblyopia treatment: defined as two acuity measurements that are 2 or more logMAR levels worse than enrollment acuity in amblyopic eye.

- Failure may be declared at any visit. Once "failure" has been declared, the patient may be treated at the investigator's discretion.

1.5 Organizational Structure and Policies

ATS2 is being coordinated by the Jaeb Center for Health Research in Tampa, Florida and funded through a cooperative agreement from the National Eye Institute. The organizational structure of the study group and study policies is detailed in the PEDIG Bylaws document.

CHAPTER 2
RANDOMIZED TRIALS

2.1 Screening and Enrollment of Patients

2.1.1 Eligibility Assessment and Informed Consent

1. A patient is considered for the study after undergoing a routine examination by an investigator (as part of standard care) that identifies amblyopia potentially meeting the eligibility criteria. As noted in subsequent sections, refractive error must be corrected with glasses (as is the case in standard patient care) before a patient can be enrolled into the trial.

2. For patients who appear eligible for the study following a "standard-care" or preliminary examination, the study will be discussed with the child's parent(s) or guardian. Parents or guardians 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.

2.1.2 Eligibility and Exclusion Criteria

1. Age < 7 years

2. For Study A, not in or within 4 months of entering first grade

3. Able to measure surrounded single optotype visual acuity using the ATS protocol
   - *this will in effect exclude all patients <2 years old and many <3 years old*

4. Amblyopia associated with strabismus (comitant or incomitant), anisometropia, or both
   - *Strabismic Amblyopia is defined as amblyopia (1) in the presence of either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum), and (2) in the absence of refractive error meeting the criteria below for combined mechanism amblyopia.*
   - *Refractive/anisometropic Amblyopia is defined as amblyopia in the presence of anisometropia ≥0.5 D of spherical equivalent or ≥1.50 D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation, which persists after at least 4 weeks of spectacle correction (if required-see section 2.1.3).*
   - *Combined Mechanism Amblyopia is defined as amblyopia in the presence of (1) either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum), and (2) anisometropia ≥1.00 D spherical equivalent or ≥1.50 D difference in astigmatism in any meridian, which persists after at least 4 weeks of spectacle correction (if required-see section 2.1.3). Note: the spherical equivalent requirement differs from that in the definition for refractive/anisometropic amblyopia.*

5. Visual acuity, measured in both eyes without cycloplegia within 7 days prior to randomization using the ATS single-surround HOTV letter protocol on the PC Vision Tester as follows:
   a. Visual acuity in the sound eye ≥20/40
   b. Visual acuity in the amblyopic eye ≤20/40 and ≥20/400
   c. Inter-eye acuity difference ≥3 logMAR lines
   - *If acuity in the amblyopic eye is 20/100-20/400, patient is eligible for trial A and if acuity is 20/40-20/80, patient is eligible for trial B*

6. No prior amblyopia therapy or if there has been prior therapy, it must meet the following criteria:
   a. no patching treatment within 6 months of enrollment and no other amblyopia treatment of any type (other than spectacles) used within one month of enrollment
   b. any treatment more than 6 months prior to enrollment is acceptable

7. No current vision therapy or orthoptics
8. No ocular cause for reduced visual acuity
   - *nystagmus per se does not exclude the patient if the above visual acuity criteria are met*
9. Cycloplegic refraction and ocular examination within 2 months prior to enrollment
10. No myopia more than a spherical equivalent of -6 D.
11. Refractive error corrected for at least 4 weeks subject to the guidelines in section 2.1.3.
12. No prior intraocular surgery
13. No known skin reactions to patch or bandage adhesives
14. Parent willing to accept either treatment, available for 4 months of follow-up, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff

2.1.3 Refractive Error

2.1.3.1 Patients with Strabismic Amblyopia

Refractive error should be corrected according to the investigator's usual routine.

2.1.3.2 Patients with Refractive/Anisometropic or Combined Mechanism Amblyopia

1. Anisometropia ≥1.00 D in spherical equivalent or ≥1.50 D of meridional difference must be treated for at least 4 weeks prior to enrollment.
   - *Lesser degrees of refractive error can be corrected at the investigator's discretion.*
   - *The spectacle correction to prescribe is left to investigator judgment. Suggested guidelines appear below.*
   - *If a patient is already wearing glasses, a new prescription is not necessary as long as (1) both the spherical equivalent and cylinder are within 0.50 of fully correcting the anisometropia and (2) the cylinder axis in both eyes is within 10 degrees of the axis in the spectacles when cylinder power is ≥ 1.00 D (if cylinder power is < 1.00 D, spectacle change is at the investigator's discretion); if these limits are exceeded, then a lens change should be prescribed and worn for at least 4 weeks before the patient can be considered for study enrollment.*
2. If 4 or more weeks of spectacle wear has improved the visual acuity in the amblyopic eye, investigator discretion is used to determine whether to continue the patient on spectacle therapy alone or whether to consider the patient for enrollment into the study.
3. Guidelines for Spectacles
   - *Full correction of anisometropia*
   - *Hypermetropia >3D corrected by either prescribing the maximum-tolerated hyperopic correction in a post-cycloplegic noncycloplegic refraction or by reducing the cycloplegic refraction by up to +1.50*
   - *Astigmatism ≥ 1.50 D in either eye corrected (full correction of astigmatism is preferred)*
   - *Myopia >3D corrected (full correction of myopia is preferred)*

2.1.4 Examination Procedures

2.1.4.1 Historical Information

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

2.1.4.2 Clinical Testing

Examination procedures include:

1. Measurement of visual acuity in both eyes (right eye first) by the ATS single-surround HOTV testing protocol on the PC Vision Tester

- *Testing must be done without cycloplegia (with spectacles if worn) within 7 days prior to randomization.*
- *Prior to the formal measurement of visual acuity, a binocular screening test can be performed on the PC Vision Tester, at investigator discretion, to determine whether the patient is capable of having visual acuity measured by the ATS protocol.*
- *In the acuity testing, an adhesive patch is to be placed on the skin over the nontested eye. If the child will not wear the patch, he or she is ineligible.*
- *Since the patient needs to be wearing spectacles that provide best visual acuity to be enrolled, trial frames/phoropter with a different correction cannot be used to measure acuity at enrollment.*
- *Use of the HOTV matching card facilitates the testing.*

2. Cycloplegic refraction as per investigator's usual routine
   - *if performed within prior 2 months, do not need to repeat at time of enrollment*

3. Ocular motility examination:
   - *measure predominant alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near; and presence of primary position nystagmus (with and without monocular occlusion)*

4. Ocular examination as per investigator's clinical routine to rule out a cause for reduced visual acuity other than amblyopia
   - *if performed within prior 2 months, do not need to repeat at time of enrollment*

If the patient has difficulty with the acuity testing, often he or she will perform better when the testing is repeated. At the investigator's discretion, acuity can be retested on the same or a subsequent day to assess eligibility.

2.1.5 Enrollment of Eligible Patients

1. 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 randomize a patient until he/she is convinced that the parent/guardian will accept either treatment regimen.

2. Treatment must commence within 48 hours following randomization; therefore, a patient should not be randomized until the both the investigator and parent are ready to start treatment.

3. The Jaeb Center will construct a separate Master Randomization List for each trial (both A and B) using a permuted block design stratified by site, which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed (see ATS2A/B Enrollment Form for steps to follow).

2.1.5.1 Delay in Enrollment

1. The ATS visual acuity testing must be performed within 7 days prior to randomization. If patient randomization is delayed beyond 7 days, the visual acuity test must be repeated to confirm eligibility and establish the baseline acuity for the study.

2. No other parts of the examination need to be repeated if they were performed within 2 months prior to randomization.

2.2 Treatment Regimens

2.2.1 Overview

Depending on the visual acuity in the amblyopic eye, a patient is randomized to one of two protocols, with the following 4-month patching regimens:

Protocol A

- 6 hours per day
- Full time (every waking hour or all but one waking hour) per day

Protocol B

- 6 hours per day
- 2 hours per day

Two study follow-up visits are required: an interim visit at 5±1 week and an outcome visit at 17± 1 week. Additional visits are at investigator discretion.

At the completion of the 17-week outcome exam, the investigator will continue to manage the patient as per his/her usual practice. If visual acuity in the amblyopia eye has improved by 3 or more logMAR lines from baseline at the 17-week visit or at a later time such that the investigator is ready to discontinue treatment, the patient may be eligible for the Amblyopia Recurrence Observational Study (see chapter 3). If eligible and the parent agrees to participate, a separate consent form will be signed.

2.2.2 Treatment Regimens

2.2.2.1 Patching

The number of hours of patching per day is prescribed based on the randomization assignment, as indicated above.

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 (see section 2.4.1).

2. The hours of patching should be continuous when possible. Periods when the child is sleeping will not be counted as patching time.
   - The assigned patching regimen is continued for the four-month study duration unless the visual acuity in the amblyopic eye improves to within one logMAR line of the acuity in the sound eye. If the acuity in the amblyopic eye improves to be the same as or one line worse than the acuity in the sound eye, patching can be continued at the initial number of hours or decreased at investigator discretion but must be at least 7 hours per week.
   - If the acuity in the amblyopic eye is better than the acuity in the sound eye, then treatment can be continued, reduced, or stopped at investigator discretion.

3. If reverse amblyopia develops, management is left to the investigator's judgment (see section 2.4.2 for guidelines).

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

5. Prior to the four-month masked exam, patients should not be prescribed additional hours of occlusion or alternate therapies for amblyopia such as filters, over-plus lenses, atropine, other cycloplegic drops, or penalizing contact lenses, even if there is no response to treatment.

6. If the investigator believes there is an overriding reason to prescribe a nonprotocol treatment, the Protocol Chair should be contacted to review the case. If there is agreement that the change is warranted, a masked visual acuity measurement of the amblyopic eye should be performed before the nonprotocol treatment is prescribed.

2.2.2.2 Visual Activities While Patching

The parent will be instructed to have the child spend at least one hour of patching time each day doing eye-hand coordination activities 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.

2.2.3 Compliance

A daily log will be maintained by patients on treatment.

1. An adhesive sticker will be placed by the child on the log on days where the protocol treatment was successfully completed. The caregivers will be asked to indicate daily the number of hours of patching.
2. These logs will be turned in to the investigator at each of the protocol visits. At each visit, the logs will be reviewed. The investigator's assessment of compliance will be recorded on the Follow-up Examination Form.

2.3 Follow-up Examinations

The two follow-up visits required for the study at 5 $\pm$ 1 weeks (Visit A) and 17 $\pm$ 1 weeks (Visit B) represent the minimum number of visits that would be performed as part of routine patient care. Additional visits are at the discretion of the investigator.

1. A Follow-up Examination Form should be faxed to the Jaeb Center for every exam (not just the minimum required exams).
2. At <u>all</u> visits (protocol-specified and unspecified visits), visual acuity is measured in both eyes (right eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol on the PC Vision Tester and ocular alignment is assessed with the SPCT.
   - *At visit B, the acuity testing will be conducted by a certified masked examiner*
3. The Amblyopia Treatment Index (questionnaire) is given to a parent or guardian to complete at visit A.
   - *The questionnaire consists of 18 questions concerning the effect of the patching on the child and parent. It is self-administered and does not require instructions from the site staff*
   - *The questionnaire should be completed <u>prior</u> to the investigator's examination of the patient, sealed in the self-addressed postage-paid envelope by the parent, and given to clinic staff for mailing to the Jaeb Center.*
   - *The questionnaire is meant for the child's parent or guardian who is responsible for seeing that the child wears the patch. If the child is brought to the visit by an individual who is not involved in placing the patch on the child and in monitoring the wearing of the patch, this is indicated on the questionnaire and it is not completed.*
4. Additional testing done at visit B: stereoacuity testing (Titmus fly, Randot, Randot Preschool) and fusion testing (Worth 4-dot).
   - *These tests may be done by a masked or unmasked individual after completion of the acuity testing.*
   - *The exam forms contain details of the specifics of the testing procedures.*

5. Additional stipulations for visit B:
   - *If it is not possible to measure visual acuity using the ATS protocol on the PC Vision Tester because either the patient is uncooperative or there is an equipment failure, the patient should return within one week for a repeat examination.*
   - *For patients being actively patched, the parent will be advised to not use the patch on the day of visit*

2.4 Adverse Events/Risks

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.

2.4.1 Patch Allergy

1. Removal of the patch overnight and coating of the skin with lubricants and emollients generally can effectively deal with this problem.
2. When a patient develops an allergic reaction serious enough to discontinue patching, the investigator should call the protocol chair to discuss the case. If patching is discontinued, then the patient should be tried with Patch Works on glasses (plano if patient not wearing spectacles).
   - *The Jaeb Center will send a spectacle-mounted occluder (Patch Works) directly to the patient.*
   - *If plano glasses are needed and either investigator does not consider this to be part of his/her standard management or the family does not have resources to cover the glasses, they will be paid for by the Jaeb Center.*

2.4.2 Reverse Amblyopia

Patching potentially could decrease the visual acuity in the sound eye, although this is almost always reversible. 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 full 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 Protocol Chairman to discuss the case and further treatment. Amblyopic treatment, other than patching, should not be prescribed prior to discussing the case with the Protocol Chair.

2.4.3 Development of Strabismus

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's and parent's decision. If amblyopia treatment is to be discontinued during the first 4 months, the Protocol Chair should be called to discuss the case and a masked examination arranged.

2.4.4 Risks of Examination Procedures

The procedures in this study are part of daily ophthalmologic practice in the United States and pose no known risks. Although the patient may receive eye drops as part of routine care, no eye drops are required during the study by the protocol.

2.4.5 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 their IRB.
3. Data on the complications of the study treatments will be tabulated regularly by the Data 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 IRB's.

2.5 Miscellaneous Considerations

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 Event/Patient Status Form.
2. Certain events are of sufficient importance that they will be reported separately on the Event/Patient Status Form. These include eye injuries or development of eye problems that might affect vision, development of serious medical problems that might affect study participation or testing results by the affected patient, and patient deaths.
3. Strabismus surgery is allowed at the discretion of the clinician. Performance of such strabismus surgery will be reported on the Event/Patient Status form.
4. Changes in spectacle correction are left to the investigator's usual routine and clinical judgment.

2.6 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.

- Two phone contacts are planned: one in the first month after enrollment and one in the fourth month prior to the outcome examination.

2.6.1 Patient Withdrawals

1. 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.
2. Termination (withdrawal) or a change of treatment does not equate with termination (withdrawal) from the study. Patients who stop or change treatment will continue to follow the study protocol for the follow-up/outcome examination.

CHAPTER 3
AMBLYOPIA RECURRENCE OBSERVATIONAL STUDY

3.1 Eligibility and Enrollment of Patients

3.1.1 Eligibility Assessment and Informed Consent

Patients meeting the criteria listed in the next section for whom the investigator believes that treatment should be discontinued are eligible for this observational study.

The study will enroll both patients who participated in one of the ATS randomized trials and other patients. Patients in ATS1 can be enrolled after their primary outcome visit at 6 months. Patients in ATS2 cannot be enrolled until their follow-up has ended at 4 months. ATS2 patients could be enrolled upon completion of their follow up in the randomized trial or at a later time.

The study will be discussed with the parent(s) or guardian of eligible patients. Parents or guardians who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the patient's routine care.

3.1.2 Eligibility and Exclusion Criteria

1. Age <8 years
2. Since its start, current cycle of amblyopia treatment has been prescribed by the ATS site and has consisted of continuous treatment for the last 3 months that is at least 2 hours/day of patching (14 hours per week) or at least one drop of atropine per week at the time of enrollment
3. Ready for cessation of treatment in investigator's judgment
4. Cause of amblyopia strabismus, anisometropia, or combined-mechanism (at start of current cycle of treatment)
   - *patients with deprivational amblyopia, including reverse amblyopia induced by treatment of amblyopia in the fellow eye, are not eligible*
5. At start of current treatment cycle, acuity in amblyopic eye 20/40 or worse with at least 3 logMAR lines inter-ocular acuity difference.
6. <u>If patient has been in ATS1 or ATS2 randomized trial</u>,
   - visual acuity in amblyopic eye at the time of enrollment into the Observational Study has improved by at least 3 logMAR lines from the ATS baseline acuity (measured using the ATS visual acuity testing protocol)
7. <u>If patient was not in ATS1 or ATS2 randomized trial,</u>
   - visual acuity in amblyopic eye at the time of enrollment into the Observational Study has improved by the equivalent of at least 3 logMAR lines from the start of the current treatment cycle (measured using the same acuity measurement technique at both time points)
   - visual acuity in amblyopic eye is at least 20/80 by ATS acuity protocol on the PC Vision Tester *(required in order to increase the probability that a 3-line improvement has occurred)*
   - visual acuity in the sound eye was <u>≥</u>20/40 at both the start of the treatment cycle and at the time of enrollment.

8. Cycloplegic refraction within past 6 months and patient wearing optimal refractive correction consistent with the guidelines of section 2.1.3.

9. Patient is available for 12 months of follow-up, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff

For analysis, the patients will be classified into one of two groups 1) immediate cessation and 2) weaning

Definitions:

- "Maximum intensity" of treatment will be individually defined (for each patient) as the maximum number of hours of patching used for at least 4 weeks during the current cycle of treatment (or maximum number of days per week of atropine used for at least 4 weeks). "Half-maximal" intensity will be calculated and based on hours per day or week of patching and days per week of atropine (e.g. "half-maximal" therapy would be 3 hours patching per day if maximal was 6 hours per day).
- "Immediate cessation" - patching or atropine of at least "half-maximal" intensity at the time of enrollment. Note: the over-riding enrollment inclusion criteria of at least 2 hours per day (14 hours per week) of patching, or at least one drop of atropine a week.
- "Weaning"- patching or atropine at less than half-maximal intensity at the time of enrollment.

3.1.3 Examination Procedures

3.1.3.1 Historical Information

Historical information to be elicited will include the following:

- date of birth
- type of amblyopia (anisometropic, strabismic, and combined)
- visual acuity in both eyes at the start of the current cycle of treatment
- age at first diagnosis of amblyopia
- date of achieving best visual acuity during current cycle of treatment
- method(s) of treatment in current cycle
- Recurrences of amblyopia prior to current cycle (*These data will only be collected if all management of amblyopia for the patient has been at the site*)

3.1.3.2 Clinical Testing

Examination procedures include:

1. Measurement of visual acuity in both eyes without cycloplegia and with spectacles (if worn) by the ATS single-surround HOTV testing protocol on the PC Vision Tester (*within 7 days prior to enrollment)*
2. Measurement of ocular deviation in primary position at distance and near by Simultaneous Prism and Cover Test (SPCT)
3. Measurement of stereoacuity (Titmus fly, Randot, Randot Preschool) and fusion (Worth 4-dot)

3.1.4 Enrollment of Eligible Patients

A patient is enrolled by entering data on the ATS website or by faxing the study enrollment form to the Jaeb Center.

3.2 Patient Management

1. At the time of enrollment, all amblyopia treatment with the exception of spectacle correction is discontinued.
2. The anisometropic aspect of refractive error must be corrected. Otherwise, refractive error is corrected as per the investigator's usual routine.
3. If amblyopia recurs and meets the study's failure criteria (see section 3.3.1), the investigator may institute any form of amblyopia therapy, which will be recorded on the follow-up exam form. Patient follow up will continue through one year, with collection of treatment and acuity data.
4. Treatment should not be reinstituted prior to a patient's meeting criteria for failure (except for the rare possibility of reverse amblyopia in which case treatment is at investigator discretion).
5. If the criteria for failure listed in section 3.3.1 are met, but the investigator believes that the acuity testing results may not be valid (e.g., patient inattention during testing) and does not reinstitute treatment, then the patient should be retested within one month.

3.3 Follow-up Examinations

Four follow-up exams are required for the study: 5 $\pm$ 1 week, 13 $\pm$ 2 weeks, 26 $\pm$ 2 weeks, and 52 $\pm$ 2 weeks. This is consistent with the minimum number of exams that would be performed in usual clinical practice. Additional visits are at the discretion of the investigator.

At each visit (both protocol-specified and additional visits), visual acuity is measured in both eyes (right eye first) by a certified examiner using the ATS single-surround HOTV visual acuity testing protocol on the PC Vision Tester.

- If the amblyopic eye acuity is 2 or more logMAR lines worse than the enrollment acuity, the testing is repeated in the amblyopic eye. The measurement may be on the same day.

A Follow-up Examination Form should be faxed to the Jaeb Center for every exam (not just the minimum required exams).

3.3.1 Definition of Recurrence (Failure)

A recurrence of amblyopia is defined as two consecutive 'valid' visual acuity measurements in the amblyopic eye that are 2 or more logMAR lines worse than the enrollment acuity (worsening from enrollment $\geq$0.2 logMAR units), in the absence of a reduction of acuity in the sound eye of 2 or more logMAR lines (on the first testing; sound eye testing does not need to be repeated). The two measurements can be on the same or different days.

Validity of the acuity measurements is left to investigator judgment. If the investigator believes that the acuity test results may not be valid, such as due to patient inattention, treatment should not be reinstituted and the patient should return for repeat acuity testing, preferably within one month. If the acuity is again decreased in the amblyopic eye by 2 or more logMAR lines, this will constitute a failure. Reinstitution of treatment will be considered evidence that the investigator believes the acuity results to be valid.

Failure may be declared at any visit (protocol-specific or additional visit). If at the 12-month visit, a patient who has not previously been classified as a failure has a decrease in visual acuity of $\geq$2 logMAR lines 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 the 12-month visit. If a refraction has not been performed within the prior six months, as per usual clinical practice it should be repeated before a patient is classified as a failure.

Once "failure" has been declared, the patient may be treated at the investigator's discretion. Follow-up will be continued through 12 months.

3.4 Risks and Alternative Treatment

The only risk involved in the study is that visual acuity in the amblyopic eye may worsen when treatment is discontinued. This risk is the same whether therapy is discontinued in the study or outside the study.

The only alternative treatment would be to discontinue therapy by a step-down protocol rather than completely discontinuing therapy at the time of enrollment. Whether the risk of worsening of visual acuity in the amblyopia eye differs with a step-down approach compared with complete cessation is unknown.

3.5 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. Three phone contacts are planned: one in the 1st month after enrollment, one in the 6th month, and one in the 12^{th} month.

A patient (and in this case the parents or guardian) may withdraw from the trial at any time. No further data will be collected on patients who withdraw from the study.

CHAPTER 4
SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

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

4.1 Randomized Trials

4.1.1 Sample Size

A sample size of 160 (80 per group) has been selected for each trial. For both trials, Monte Carlo simulations were used to estimate the sample size from projected baseline and outcome visual acuity data assuming a type I error rate of 5% (two-tailed). For trial A (severe amblyopia), the sample size estimation assumes a standard deviation of 0.338 for the 4-month acuity scores, mean difference between groups in two group comparisons of 0.2 logMAR units, and correlation between the baseline and outcome scores of 0.38. For trial B (moderate amblyopia), the sample size estimation assumes a standard deviation of 0.169 for the 4-month acuity scores, mean difference between groups in two-group comparisons of 0.1 logMAR units, and correlation between the baseline and outcome scores of 0.38. The sample size of 160 (80 per group) for each trial has been selected to provide 97% power for the primary analysis and 80% power for two subgroup analyses based on the cause of amblyopia (two approximately equal size subgroups: [1] *strabismus with a deviation $\geq$ 5 pd or a history of strabismus surgery, with or without anisometropia and [2] strabismus with a deviation < 5 pd and no history of strabismus surgery, with or without anisometropia, or anisometropia alone)*. The sample size estimates assume 5% loss to follow up. With 90% power, a treatment group difference in mean logMAR acuity of .16 can be detected in trial A and of .08 can be detected in trial B.

The number of patients enrolled in each trial who are either (1) 6-<7 years in age or (2) received prior amblyopia therapy (other than spectacle correction of refractive error) will be tracked. If enrollment exceeds approximately 25% for either of these in a trial, recruitment may be continued until 120 patients (75% of 160) not meeting the criterion are enrolled.

4.1.2 Primary Analysis

In each trial, the primary analysis will be a comparison of logMAR visual acuity scores in the two treatment groups obtained four months after randomization, adjusted for baseline visual acuity scores in an analysis of covariance (ANCOVA) model.

4.2 Amblyopia Recurrence Observational Study

4.2.1 Sample Size

The sample size will include 100 patients meeting the criteria for "immediate cessation" (patching or atropine at maximal intensity within one week of enrollment or at least "half maximal" intensity within one week of enrollment, with no previous reduction to less than half maximal). This sample size is based on an estimated amblyopia recurrence rate of 40% and a 95% confidence interval limit of 10%. During the time period of the recruitment of these 100 patients, no limit will be placed on the recruitment of patients meeting criteria for "weaning" (patching or atropine at less than half-maximal intensity on enrollment or within one week of enrollment).

4.2.2 Analysis Plan

The proportions of patients and 95% confidence intervals will be computed for a recurrence (failure) by 12 months overall and in each of the two subgroups (immediate cessation and weaning). Exploratory analyses will be conducted to identify factors associated with a recurrence.