AMBLYOPIA TREATMENT STUDY
ATS16

Augmenting Atropine Treatment for Amblyopia

PROTOCOL

Version 1.0

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Contact Information

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Chapter 1: Background and Summary

The study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and is being coordinated by the Jaeb Center for Health Research in Tampa, Florida. The study is funded through a cooperative agreement from the National Eye Institute.

1.1 Objective

This study is designed to evaluate the effectiveness of adding a plano lens to weekend atropine after visual acuity has stabilized with weekend atropine but amblyopia is still present. Children ages 3 to <8 years with visual acuity of 20/50 to 20/400 in the amblyopic eye will be enrolled in a run-in phase with weekend atropine until no improvement, followed by randomization of eligible patients to weekend atropine treatment with a plano lens over the sound eye versus without a plano lens over the sound eye. The primary objective is to determine if adding a plano lens to weekend atropine will improve visual acuity in patients with amblyopia still present after visual acuity has stabilized with initial treatment.

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. Both patching and atropine are accepted treatment modalities for the management of moderate amblyopia in children.[1] Many practitioners prescribe weekend atropine as initial therapy for amblyopia. However, many children fail to achieve normal visual acuity in the amblyopic eye after treatment with this regimen. In a randomized trial conducted by PEDIG comparing atropine regimens, 58 of 83 patients with moderate amblyopia (70%) had amblyopic eye visual acuity of 20/32 or worse after 4 months of treatment with weekend atropine.[2] In another PEDIG randomized trial comparing atropine with a plano lens versus without a plano lens for initial treatment of amblyopia, 60 of 84 patients with moderate amblyopia (71%) had amblyopic eye visual acuity of 20/32 or worse after 16 weeks of treatment with weekend atropine.[3] When improvement stops after initial therapy and amblyopia is still present, treatment options include increasing the dosage of current treatment, switching to another treatment, maintaining the same treatment and dosage, or combining treatments. Many clinicians will add a plano lens over the sound eye to atropine treatment, in part because families using atropine have become comfortable with its use. This option is limited to children with hypermetropia in the sound eye. However, it is unknown whether adding a plano lens over the sound eye will improve amblyopic eye visual acuity more than continuing atropine alone in patients who have shown no improvement after initial treatment with atropine. In a PEDIG randomized trial comparing patching to atropine for initial treatment of amblyopia, a plano lens was prescribed for the sound eye for 55 patients who had not improved to 20/30 or at least 3 lines after 4 months of daily atropine use.[1, 4] Their mean acuity improvement prior to using the plano lens was 1.0 line, compared with 1.6 lines after prescribing the plano lens. We are unaware of any reports of the response of treatment of amblyopia still present after initial treatment with weekend atropine.

1.3 Synopsis of Study Design

The study consists of two phases:

1) A run-in phase during which all patients are treated with atropine.
    - Patients may be enrolled either at the initiation of atropine treatment or during the course of treatment, provided that the prescribed treatment regimen to that point has been weekend or daily atropine.

2) A randomized trial, beginning after visual acuity has stabilized and amblyopia is still present, in which the patient is randomized to either continue weekend atropine or to use a plano lens over the sound eye with weekend atropine.

Major Eligibility Criteria for Run-in Phase (see section 2.2 for a complete listing)

- Age 3 to < 8 years
- Amblyopia associated with strabismus, anisometropia, or both
- Visual acuity in the amblyopic eye between 20/50 and 20/400 inclusive
- Visual acuity in the sound eye 20/32 or better and inter-eye acuity difference ≥3 logMAR lines
- Amblyopia treatment within the past 6 months subject to the following stipulations:
  - No more than 6 weeks of any amblyopia treatment other than spectacles (except for patients being treated with atropine who are entering the study on treatment)
  - No *simultaneous* treatment with patching and atropine
  - No use of atropine in combination with the sound eye spectacle lens reduced by more than 1.50 D
  - Maximum level of treatment within the past 6 months:
    - Patching: up to 2 hours daily
    - Atropine: up to once daily
- Wearing spectacles with optimal correction (if amblyopic eye acuity is 20/80 or better, then VA must be stable in glasses; if amblyopic eye acuity is 20/100 or worse, then spectacles and atropine can be initiated simultaneously).
- Hypermetropia and spectacle correction in sound eye of +1.50 D or more

Eligibility Criteria for Randomization:

- Amblyopic eye acuity of 20/40 to 20/160 with an inter-ocular difference of ≥2 lines, or amblyopic eye acuity of 20/32 with 3 lines of IOD.

Atropine Run-In Phase

At enrollment, patients will begin (or continue, in circumstances described above) weekend atropine, and they will be followed every 6 weeks. Participation in this phase ends when there has been no improvement of one or more lines in amblyopic eye acuity between 2 consecutive visits at least 6 weeks apart, confirmed by a re-test, and patients have received at least 12 weeks of atropine treatment.

Randomized Treatment Groups

When there has been no improvement with weekend atropine, eligible patients will be randomized to one of two treatment regimens:

- Intensified treatment: Weekend atropine 1% with plano lens over the sound eye
- Control: Weekend atropine 1%

Sample Size

Seventy-nine patients will be randomized in each of the two treatment groups, for a total of 158 patients. This sample size has 90% power to detect a difference if the true difference in change from baseline between groups is 0.075 logMAR at 10 weeks, with 2-sided type I error of 5%.

RCT Contact and Visit Schedule

- Phone call 5 weeks after randomization
- Primary outcome visit 10 weeks after randomization. Patients will return for an additional off-atropine visit 2 weeks later.

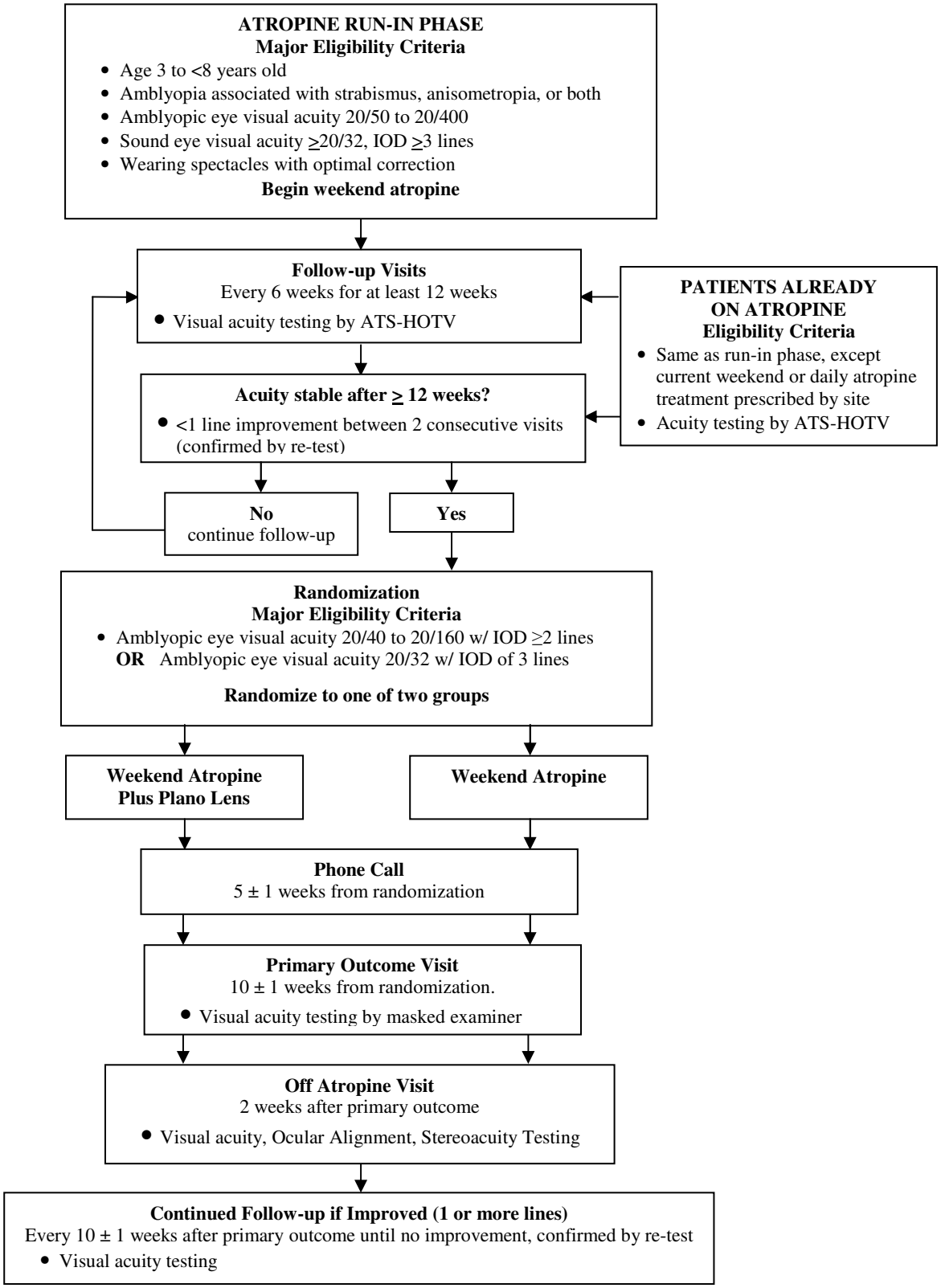
- If amblyopic eye acuity improved by ≥1 line at primary outcome, follow-up visits at 10 week intervals until no improvement, confirmed by a re-test

Primary Analysis

The primary outcome is amblyopic eye visual acuity 10 weeks after randomization.

The primary analytic approach for the amblyopic eye acuity will be a treatment group comparison of the mean amblyopic eye acuity adjusted for baseline acuity using an analysis of covariance.

1.4 Study Summary Flow Chart



Chapter 2: Patient Enrollment

2.1 Eligibility Assessment and Informed Consent

A minimum of 158 patients are expected to be enrolled with a goal to enroll an appropriate representation of minorities. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Patients who have signed an informed consent form can be randomized up until the end date, which means the minimum recruitment goal might be exceeded. The maximum number of randomized patients will be 178.

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

For patients who appear eligible for the study following a "standard-care" 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 brochure and a copy of the consent form. Written informed consent will be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the patient's routine care.

2.2 Eligibility and Exclusion Criteria

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

1. Age 3 to < 8 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
     - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
   - Criteria for anisometropia: At least one of the following criteria must be met:
     - ≥0.50 D difference between eyes in spherical equivalent
     - ≥1.50 D difference between eyes in astigmatism in any meridian
3. Amblyopic eye has no myopia (-0.25 D or more spherical equivalent).
4. Visual acuity, measured in each eye without cycloplegia (see exception for atropinized sound eye in section 2.3.2) within 7 days prior to enrollment using the ATS single-surround HOTV letter protocol as follows:
   - Visual acuity in the amblyopic eye between 20/50 and 20/400 inclusive
   - Visual acuity in the sound eye 20/32 or better
   - Inter-eye acuity difference ≥3 logMAR lines (i.e., amblyopic eye acuity at least 3 lines worse than sound eye acuity)
5. Amblyopia treatment within the past 6 months subject to the following stipulations:
   - No more than 6 weeks of any amblyopia treatment other than spectacles (except for patients being treated with atropine who are entering the study on treatment)
   - No *simultaneous* treatment with patching and atropine

- No use of atropine in combination with the sound eye spectacle lens reduced by more than 1.50 D
- Maximum level of treatment within the past 6 months:
  - Patching: up to 2 hours daily
  - Atropine: up to once daily

6. Spectacle correction for measurement of enrollment visual acuity must meet the following criteria and be based on a cycloplegic refraction that is no more than 6 months old:
   a. Requirements for spectacle correction:
      1) Hypermetropia must not be undercorrected by more than +1.50 D spherical equivalent, and the reduction in plus sphere must be symmetric in the two eyes.
      2) Correction of the sound eye must have spherical equivalent of +1.50 D or more.
      3) For patients meeting criteria for only strabismus (see 2.2 #2 above), spectacle correction is otherwise at investigator discretion.
      4) For patients meeting criteria for anisometropia or combined-mechanism (see 2.2 #2 above)
         - Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
         - Cylinder power in both eyes must be within 0.50 D of fully correcting the astigmatism
         - Cylinder axis in the spectacle lenses in both eyes must be within 6 degrees of the axis of the cycloplegic refraction when cylinder power is $\geq$ 1.00 D
   b. For patients with enrollment acuity of 20/80 or better, spectacles meeting above criteria must be worn either:
      1) for 16 weeks immediately prior to enrollment, or
      2) until visual acuity in amblyopic eye is stable (defined as two consecutive visual acuity measurements by the same testing method at least 4 weeks apart with no improvement of one line or more)
         - An acuity measurement done any of the following ways may be considered the first of two consecutive measurements: 1) in current glasses, 2) in trial frames with full correction of hypermetropia with cycloplegia, or 3) in new glasses. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*
   c. For patients with enrollment acuity of 20/100 or worse, initiating treatment with spectacles and atropine simultaneously is allowed
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. Ocular examination within 6 months prior to enrollment
10. No prior intraocular or refractive surgery
11. No known allergy to atropine or other cycloplegic drugs
12. Down Syndrome not present
13. Parent willing to accept randomized treatment, has home phone (or access to phone), and willing to be contacted by Jaeb Center staff
14. Parent does not anticipate relocation outside area of active study site

2.3 Examination Procedures

2.3.1 Historical Information

Historical information elicited will include the following: date of birth, gender, ethnicity, iris color, prior amblyopia therapy (e.g., glasses, patching, pharmacologic, Bangerter filters), current spectacle correction, and history of allergy to cycloplegic eye drops.

2.3.2 Clinical Testing

Examination procedures include:

1. Visual Acuity
   - Measurement of visual acuity in each eye (right eye first) by the ATS single-surround HOTV testing protocol.
   - The ATS-HOTV visual acuity protocol must be used throughout the study. The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual. Aspects of the testing protocol that are specific to this study are:
     - Testing of the amblyopic eye must be done without cycloplegia (with spectacles, if worn) no more than 7 days prior to enrollment.
     - Patients currently wearing spectacles must have amblyopic eye acuity measured while wearing spectacles - trial frames or phoropter cannot be used.
     - If the sound eye is atropinized, then the best-corrected (based on the most recent refraction) sound eye visual acuity will be measured by placing the appropriate refractive correction before the sound eye.
2. Ocular motility examination
   - Measurement of alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near
   - If performed within prior 7 days, it does not need to be repeated at time of enrollment
3. Ocular Examination
   - Complete ocular examination, including dilated fundus examination, to rule out a cause for reduced visual acuity other than amblyopia.
   - If performed within prior 6 months, it does not need to be repeated at time of enrollment
4. Cycloplegic Refraction
   - Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
   - If performed within prior 6 months, it does not need to be repeated at time of enrollment

Chapter 3: Atropine Run-In Phase

3.1 Atropine Run-In Phase Follow-up Visits

After enrollment, weekend atropine is prescribed. Those children using daily atropine at enrollment will be switched to weekend atropine. During the run-in phase, follow-up visits will occur every 6 weeks as long as both of the following criteria are met:

- Amblyopic eye has improved at least one line from the previous visit
- Amblyopia is still present, defined as amblyopic eye acuity at least one line worse than the best sound eye acuity that has been recorded at any visit during the study

Note: If the amblyopic eye acuity meets the above criteria, follow-up will continue every 6 weeks even if the sound eye acuity has worsened from the prior visit.

At each follow-up visit, visual acuity will be tested using the ATS HOTV visual acuity testing protocol with a study certified visual acuity tester. If the amblyopic eye acuity has not improved from the prior visit, acuity should be re-tested.

- If on the re-test there is still no improvement from the prior visit, and the prior visit was at least six weeks ago and the patient was on atropine for at least 12 weeks then the patient has completed the Atropine Run-In Phase of the study, otherwise, the patient continues in follow-up.
- The better of the two amblyopic eye visual acuities at the last visit of the Atropine Run-In Phase serves as the baseline amblyopic eye acuity for the Randomized Trial.

If a re-test is required and acuity improves on the re-test, then the re-test acuity serves as the value to which the next visit is compared when judging improvement.

Patients may be enrolled into the Atropine Run-In Phase either at the initiation of atropine treatment or during the course of treatment, provided that the prescribed treatment regimen to that point has been weekend or daily atropine.

3.2 Randomization After Completion of the Atropine Run-In Phase

After patients complete the Atropine Run-In Phase of the study, eligibility for randomization depends on amblyopic eye acuity, inter-ocular difference, and compliance with treatment.

Eligibility Criteria for Randomization:

- Amblyopic eye acuity of 20/40 to 20/160 with an inter-ocular difference of $\geq$2 lines, or amblyopic eye acuity of 20/32 with 3 lines of IOD.
- Compliance with weekend atropine treatment based on investigator judgment.

Children who do not meet the above criteria will end study participation.

3.3 Patients Who Skip the Atropine Run-In Phase

Some patients will enter the randomized trial phase of the study without participating in the Atropine Run-In Phase. These patients must have met the same applicable criteria for eligibility (see sections 2.2 and 3.2.) and must have had no improvement in amblyopic eye visual acuity between 2 visits at

least 6 weeks apart using the ATS HOTV protocol, confirmed by a re-test. These patients must have been treated for at least 12 weeks with weekend or daily atropine by a study investigator.

For patients who skip the Atropine Run-In Phase, visual acuity will be tested in each eye using the ATS HOTV visual acuity testing protocol using a study certified visual acuity tester. The testing (and re-testing to confirm no improvement) of the amblyopic eye must be performed without cycloplegia and with the patient wearing spectacles if prescribed (i.e., trial frames cannot be used). The better of the two amblyopic eye visual acuities will serve as the baseline acuity for the Randomized Trial. If the sound eye is atropinized, then the best-corrected (based on the most recent refraction) sound eye visual acuity will be measured by placing the appropriate refractive correction before the sound eye.

Chapter 4: Randomized Trial Phase

4.1 Randomized Treatment Groups

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

- Intensified treatment group: Weekend atropine 1% and spectacles with plano lens over sound eye
- Control group: Weekend atropine with spectacle correction

For both the intensified treatment group and the control group:

- Treatment is continued until there is no further improvement in amblyopic eye acuity (improvement defined as ≥1 line) between two consecutive 10-week visits, confirmed by a re-test. Once there is no improvement of one or more lines, the patient's participation in the study is over and treatment is at investigator discretion.

Notes

1. The study will be providing atropine for all patients and new spectacles for those randomized to the plano lens group.
2. Children will be encouraged to wear a hat with a brim for outdoor activities. Nonprescription sunglasses, clip-ons, or flip-ups will be provided by the study.
3. Morning is the preferred time for administration of atropine. However, it is acceptable to administer the atropine at night if the parent/guardian has an overriding reason for it.
4. If an allergy to atropine develops, the patient can be switched to homatropine 5% after discussion with the Protocol Chair.
5. If a patient is noncompliant with treatment, the parents should be encouraged to persist with their efforts to treat to the best of their ability.
6. If a child is having difficulty in school because of treatment, the Protocol Chair should be contacted.
7. Prior to deviating from the treatment protocols or prescribing non-protocol treatment, the situation should be discussed with the Protocol Chair.

4.2 New Spectacles Prescription upon Randomization

Patients randomized to the plano lens group will be given new, study-paid spectacles (frames and lenses) upon randomization. The amblyopic eye lens prescription will be identical to the current correction and the sound eye lens prescription will be "plano." The cost of any spectacle changes prior to randomization is not covered by the study.

The parents of children receiving new glasses with the plano lens will be encouraged to go to the study optician within 48 hours to have the glasses made. Every effort should be made to have the child wearing his/her new glasses within 4 days.

Parents of all patients randomized to the atropine plus plano lens group will be given a postage paid box to return the child's original pair of glasses to the site after they pick up the new glasses with the plano lens from the study optician. The site will return the original pair of glasses to the child at the

time of the 10-week primary outcome exam to wear between that exam and the off-atropine exam two weeks later.

4.3 Randomization of Eligible Patients

1. Once a patient is randomized, that patient will be included in the analysis regardless of whether the assigned treatment is received or not. Thus, the investigator must not randomize a patient until he/she is convinced that the parent/guardian will accept and comply with either of the treatment regimens. Regardless of whether the patient receives the assigned treatment or not, the patient is still considered enrolled in the study and every effort should be made to perform the follow-up examinations according to the study protocol.
2. The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by site and treatment at enrollment (weekend or daily atropine), which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed.

4.3.1 Delay in Randomization

1. Visual acuity testing and the ocular motility examination must be performed no more than 7 days prior to randomization. If randomization is delayed beyond 7 days, then these tests must be repeated to confirm eligibility and establish the baseline measures for the study.
2. No other parts of the examination (including the refraction) need to be repeated if they were performed within 6 months prior to randomization.

4.3.2 Compliance

A calendar log will be maintained by all families. These logs will be reviewed at each of the protocol visits. The investigator's assessment of compliance will be recorded on the Follow-up Examination Form.

4.4 Follow-up Examinations

All patients will have the following study visits / interactions after randomization:

- 5 weeks after randomization: telephone call
- 10 ± 1 weeks after randomization: primary outcome visit. Atropine discontinued. For patients in the plano lens group, glasses with the correct lenses will be given back and the plano glasses will be taken away.
- 12 ± 1 weeks after randomization: off-atropine outcome visit
- For patients whose amblyopic eye acuity has improved by ≥1 line at the 10-week primary outcome visit, atropine will be restarted. For patients in the plano lens group, glasses with plano lens will be reinstituted. Visits will occur every 10 ± 1 weeks until no improvement of one or more lines, confirmed by a re-test, at which point study participation ends and treatment is at investigator discretion.

Test	Visit / Interaction				
	Baseline	*5 wk phone call*	*Primary Outcome 10 ± 1 wk*	*Off-atropine Outcome 12 ± 1 wk*	*Every 10 ± 1 wks after primary outcome***
Telephone call		X			
Distance acuity each eye*	X		X	X	X
Ocular alignment	X			X	X
Titmus Fly				X	
Randot Preschool Test				X	

*Using ATS single-surround HOTV acuity testing protocol on a study certified visual acuity tester. The acuity testing at the 10-week primary outcome visit will be done by a masked examiner.

**For patients whose amblyopic eye acuity has improved by ≥1 line at the 10-week primary outcome visit. Visits occur every 10 ± 1 weeks after the primary outcome exam until no improvement of one or more lines.

Additional visits can be performed at the discretion of the investigator. A Follow-up Examination Form should be completed on the study website for every exam (not just the minimum required exams).

4.4.1 Telephone Call

Parents will be contacted by the coordinating center via telephone 5 weeks following randomization to answer any questions and to encourage compliance with treatment.

4.4.2 Primary Outcome Visit

The primary outcome visit will occur at 10 ± 1 weeks. Atropine will be discontinued at this visit.

Testing will include the following:

1. Visual acuity
   - Measured in each eye (right eye first) by a certified masked examiner using the ATS single-surround HOTV acuity protocol on study certified visual acuity tester.
   - The best-corrected acuity of the atropinized sound eye will be measured by placing the appropriate refractive correction before the sound eye (e.g., using lenses in trial frames if needed)
   - Children who were randomized to receive atropine plus a plano lens will be tested using their old glasses for the primary outcome exam and any additional exams.
2. Re-testing of visual acuity in the amblyopic eye (if indicated)
   - If amblyopic eye visual acuity has not improved from randomization by at least one line, then it will be re-tested.
   - The results of the re-test will be used only to determine if the patient will continue study participation with the same study-mandated treatment. The first visual acuity will be used as the primary outcome visual acuity. If neither the test nor the re-test is one line better than the visual acuity at randomization, then study participation ends after the post-primary outcome examination.

4.4.3 Off-Atropine Outcome Visit

The off-atropine primary outcome visit will occur at 12 ± 1 weeks, 2 weeks after atropine has been discontinued at the primary outcome visit. For those patients continuing in study follow-up, atropine will be restarted after this visit; patients who were randomized to receive atropine plus a plano lens will reinstitute wearing the glasses with a plano lens. The original pair of glasses will be kept by the site and returned at the end of the study.

Testing will include the following:

1. Visual acuity
   - Measured in each eye (right eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol on a study certified visual acuity tester. For those children in the plano lens group, the old glasses without the plano lens will be used for acuity testing.
2. Titmus fly and Randot Preschool Stereoacuity test
3. Ocular alignment assessed with the SPCT
4. Re-testing of visual acuity in the sound eye (if indicated)
   - If sound eye visual acuity is reduced by one or more lines from its baseline acuity, then it will be re-tested.
     - If the better sound eye visual acuity of the test and the re-test is decreased by one line from baseline, and if amblyopic eye acuity improved by $\geq$ 1 line at the primary outcome visit, then the patient will continue with the same study-mandated treatment.
     - If the better sound eye visual acuity of the test and re-test is 2 or more lines down from baseline, then a cycloplegic refraction should be performed, and if a change in the refraction has occurred, then the appropriate lenses should be placed in trial frames/phoropter, and the acuity should be re-tested.
       - If the best-corrected acuity is still reduced by 2 or more lines from baseline and there has been a significant change in refraction (as defined in Section 2.2 #6), then a change in spectacle lens should be prescribed (the study will pay for this change).
       - If the best sound eye acuity at the outcome exam is decreased 2 or more lines from baseline, then study-mandated treatment may end (per investigator discretion), and the patient should return in 5 weeks to recheck the sound eye acuity. This additional visit will occur regardless of whether there was a change in sound eye refraction and/or there was an improvement in the amblyopic eye at the primary outcome exam.

4.4.4 Follow-Up Visits after the Primary and Off-Atropine Outcome Visits

For patients in either treatment group with at least one line of improvement in amblyopic eye acuity at the primary outcome examination, follow-up visits will occur every 10 ± 1 weeks after the primary outcome exam until there is no improvement of one or more lines.

Testing will include the following:

1. Visual Acuity
   - Measured in each eye (right eye first) by a certified examiner using the ATS single-surround HOTV acuity protocol on a study certified visual acuity tester.
   - The best-corrected acuity of the atropinized sound eye will be measured by placing the appropriate refractive correction (equal to the most recent cycloplegic refraction) before the sound eye (e.g., using lenses in trial frames if needed).
   - Visual acuity in the amblyopic eye will be re-tested if visual acuity has not improved from the last visit by at least one line.
   - Visual acuity in the sound eye will be re-tested if visual acuity has decreased by one or more lines from baseline, using the same protocol as the 12-week off-atropine outcome examination – see section 4.4.3.

Study participation will end only after a follow-up visit at which amblyopic eye acuity shows no improvement of one or more lines on both an initial test and on a confirmatory re-test (or at investigator discretion if there is a reduction in best sound eye acuity of $\geq$ 2 lines from baseline). For the first follow-up visit after the 12-week off-atropine outcome exam, the amblyopic eye acuity will be compared to the acuity at the primary outcome visit for the purpose of determining improvement.

When study participation ends for patients in the 'plano' group, the plano lens may be replaced at investigator discretion with a lens of proper correction purchased by the study.

Chapter 5: Miscellaneous Considerations

5.1 Management of Optical Correction

A refraction should be performed at any time the investigator suspects that refractive error may not be optimally corrected. A change in spectacle correction is at investigator discretion.

5.2 Management of Strabismus

Strabismus surgery should not be done until after the 12-week off-atropine outcome visit has been completed. Surgery will be recorded in the comment section of the Follow-up Examination Form.

5.3 Worsening of Visual Acuity in the Amblyopic Eye

If visual acuity should worsen in the amblyopic eye (or in the sound eye and does not recover with cessation or reversal of treatment), the investigator should evaluate this condition using best clinical judgment and perform whatever work-up is clinically indicated to assess for an alternate cause (i.e., other than amblyopia) for the visual loss. Patients found to have a cause other than amblyopia that fully explains the visual loss (i.e., amblyopia was never present) will be dropped from the study.

5.4 Patient Withdrawals

A parent or guardian may withdraw a patient from the trial at any time. This is expected to be a very infrequent occurrence in this trial in view of the testing procedures' similarity to routine clinical practice. If the parents or guardian indicate that they want to withdraw the child from the study, the investigator should attempt to speak with them to determine the reason.

5.5 Risks

There are no risks involved in this study that would not be part of usual care in which the study treatments were administered.

5.5.1 Risks of Examination Procedures

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

5.5.2 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.

5.5.3 Side Effects of Treatment

1. Atropine 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- see section 5.5.4.

2. Atropine could precipitate the development of an ocular deviation. See section 5.5.5.

3. Following atropine, 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 and irritability. These effects are very

uncommon using the dosage schedule in this protocol as noted in the previous studies of atropine treatment. In ATS1,[1] 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%). 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. Ocular side effects in ATS4, most commonly light sensitivity, were reported by 13 patients (16%) in the daily group and 25 patients (29%) in the weekend group.[4] However, these symptoms did not lead to a change in treatment. Facial flushing and fever were reported for 2 patients in the daily group; one of these patients remained on atropine and the other was switched to homatropine.

4. 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 several months 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.[5-8] To minimize risks from pupil dilation, sunglasses, clip-ons, or flip-ups will be provided. Hats with brims or visors will be encouraged.

5. When a patient develops adverse effects serious enough to discontinue atropine prior to the primary outcome exam, the investigator should call the Protocol Chair to discuss the case. If atropine is discontinued, then the patient could be switched to homatropine 5%. The following guidelines should be followed after discussion with the Protocol Chair:
    - If a patient has a serious systemic adverse effect of atropine (such as seizure), an atropine-like drug should not be prescribed.
    - If a patient has mild effects that may be due to atropine such as facial flushing, then homatropine should be substituted. Initially, one drop is given. If there is no adverse effect in three days, then a second drop is given. If there is no problem in three days, then weekend homatropine is started. Drops should be administered in the morning.

5.5.4 Reverse Amblyopia

Atropine could decrease the visual acuity in the sound eye, although this is almost always reversible. In ATS1, results were inconclusive as to whether atropine produced a transient decrease in sound eye acuity. However, the results indicated that treatment did not cause a permanent reduction in sound eye acuity. After two years of follow up, there was no difference in sound eye acuity between the two treatment groups.

In ATS1, a reduction in sound eye visual acuity (2 or more lines) occurred at 6 months more frequently when a plano lens was prescribed in addition to atropine (7 of 43, 16%) compared with treatment with atropine alone (4 of 123, 3%; P=0.01). However, after longer follow-up the sound eye of only one patient treated with atropine alone and no patient treated with atropine plus the plano lens was worse than baseline.

The diagnosis and management of reverse amblyopia at each of the study visits is left to the investigator's judgment. At all post-randomization visits (if indicated), a protocol will be followed for re-testing and evaluating the sound eye if it has reduced vision (see section 4.4.3).

5.5.5 Development of Strabismus

The study treatment could precipitate the development of a new manifest ocular deviation (e.g., esotropia). If this occurs, the parent(s) will be advised to have the patient see the investigator as soon as possible. If a new deviation is confirmed on examination, the decision as to whether to continue or discontinue therapy will be left to the investigator. If amblyopia treatment is to be discontinued prior to the primary outcome exam, then the Protocol Chair should be called to discuss the situation. The development of a new heterotropia is an accepted risk of standard-care amblyopia therapy. However, previous studies suggest that resolution of pre-existing strabismus during amblyopia treatment occurs as often as development of new strabismus. In ATS1, new strabismus occurred in 13% of patching patients and in 13% of those using atropine. Twenty-one percent of patients had resolution of their preexisting strabismus with treatment. In ATS4, 10% of patients had a new strabismus or a worsening of preexisting strabismus by $\geq$ 10 PD, and 8% were found to have resolution of preexisting strabismus or reduction in their strabismic angle by $\geq$ 10 PD. The risk of developing strabismus in this study is no greater than it would be with standard care of amblyopia.

Strabismus surgery is allowed at the discretion of the clinician if medically indicated following the 12-week off-atropine outcome visit.

5.5.6 Risk Assessment

It is the investigators' opinion that the protocol's level of risk falls under DHHS 46.404 which is research not involving greater than minimal risk.

5.6 Reporting of Adverse Events

Each investigator is responsible for informing his/her IRB of serious treatment-related adverse events and for abiding by any other reporting requirements specific to his/her IRB.

Data on the complications of the study treatments will be tabulated regularly by the Coordinating Center for review by the Data and Safety and Monitoring Committee. Serious, treatment-related complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

5.7 Patient Payments

The parent/guardian of each patient will be compensated $30 for each run-in phase follow-up visit, and $30 per visit for completion of the randomization visit, the primary outcome visit, and the 12-week off-atropine outcome visit. For patients remaining in follow-up after the 12-week visit, $30 will be paid for each 10-week interval visit, up to an additional $120 (4 exams). If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $30 and the patient will be unable to complete the visit without reimbursement of travel expenses. All payments will be made by the Jaeb Center in the month following the date of each completed visit.

5.8 Study Costs

The following will be provided by the study at no charge:

- Atropine eye drops.
- Non-prescription sunglasses or clip-on sunglasses if needed.
- Glasses if randomized to the atropine plus plano lens group.
- Reading glasses if needed for schoolwork.
- New lenses if the vision in the good eye worsens and the glasses prescription changes.

The study will pay for visits and testing that would not be done if the patient was not part of the study (research related visits). The patient or his/her insurance company will be responsible for the costs of visits that would be needed whether they were in the study or not (standard care visits).

5.9 Discontinuation of Study

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

5.10 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. The Jaeb Center will maintain direct contact with the parents or guardian of each patient. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the family and to help coordinate scheduling of the outcome examination. One phone contact is planned for each patient 5 weeks after randomization. Additional phone contacts will be made if necessary to facilitate the scheduling of the patient for follow-up visits. A patient newsletter, study updates, and a study logo item may be sent. Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients.

Chapter 6: Sample Size Estimation and Statistical Analysis

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan, which will supersede these sections when it is finalized.

6.1 Primary Analysis for Efficacy

The study is evaluating 2 management approaches for amblyopia in patients already treated with weekend atropine:

1. Continued weekend atropine 1%
2. Intensified treatment: Weekend atropine 1% with plano lens

The primary analysis will be a treatment group comparison of logMAR visual acuity scores obtained 10 weeks after randomization, adjusted for baseline acuity scores in an analysis of covariance (ANCOVA) model.

The primary analysis will follow the intent-to-treat principle. Data will be included only from patients who complete the 10-week outcome. There will be no imputation of data for patients who are lost to follow-up or withdraw from the study prior to the 10-week outcome. In a secondary analysis, imputation methods for missing data will be assessed (such as last-observation-carried-forward and multiple imputation) for consistency with the primary analysis. A separate analysis also will be conducted including only patients whose outcome exams were performed within the time window for the visit.

6.2 Secondary Efficacy Analyses

6.2.1 Visual Acuity Defined as a Binary Outcome

A secondary analysis will be a treatment group comparison of the proportion of patients who have improved by 2 or more logMAR visual acuity lines 10 weeks after randomization for each treatment group, adjusted for baseline acuity scores using logistic regression.

6.2.2 Follow-up after the Primary Outcome

Patients in both groups who have improved by 1 or more lines from baseline to the 10-week outcome exam will continue in the study. Visits will occur every 10 ± 1 weeks until there is no improvement of one or more lines. A secondary analysis will be a treatment group comparison of the proportion of patients with at least two logMAR lines of visual acuity improvement between randomization and the visual acuity at the last study visit using logistic regression, adjusting for baseline visual acuity. An additional secondary analysis will be a treatment group comparison of logMAR visual acuity scores in the amblyopic eye at the last study visit, adjusted for baseline visual acuity scores in an analysis of covariance (ANCOVA) model.

6.2.3 Treatment Effect in Subgroups

The treatment effect in subgroups based on baseline factors will also be assessed in exploratory analyses. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. In the absence of an overall study difference, these subgroup analyses will be interpreted with caution.

The subgroups of interest are those based on visual acuity at the time of randomization, visual acuity at the time of initial treatment, cause of amblyopia, length of prior treatment, maximum amount of prior treatment (weekend vs daily), and age at randomization.

In accordance with NIH guidelines, a subgroup analysis of treatment effect according to gender, as well as race/ethnicity, will be conducted. However, based on results from previous ATS studies, a treatment effect by these variables is not expected.

The general approach for these exploratory analyses will be to repeat the primary analysis within each subgroup.

6.2.4 Stereoacuity

Differences between treatment groups in stereoacuity measured at the 12-week off-atropine outcome visit will be assessed using a comparison of the distributions with the exact Wilcoxon rank sum test.

6.3 Primary Analysis for Safety

6.3.1 Sound Eye Acuity Data

The loss of 2 or more lines in sound eye visual acuity from baseline to the 10-week masked exam will be tabulated for each treatment group.

6.3.2 Ocular Alignment

Ocular alignment will be assessed at baseline and at 10 weeks after randomization. Development of a new strabismus (no tropia at baseline and the presence of near and/or distance tropia at follow-up) or an increase from baseline $\geq$ 10 PD will be tabulated by treatment group. Similarly, disappearance of a heterotropia and a decrease in the angle of a preexisting strabismus by $\geq$ 10 PD will be tabulated.

6.4 Sample Size

We are unaware of any previous literature on the response to treatment of amblyopia still present after initial treatment with weekend atropine. The sample size calculations were based on amblyopic eye visual acuity data in a cohort of patients initially treated with weekend atropine from our previous ATS4 and ATS8 studies.[2, 3] Patients in these studies were either randomized to weekend versus daily atropine or weekend atropine versus weekend atropine with a plano lens over the sound eye for the initial treatment of amblyopia. In ATS4, patients had office visits at 5 and 17 weeks following randomization. In ATS8, patients had office visits at 5, 10, and 18 weeks following randomization. Based on improvement in visual acuity among patients defined as stable, we assumed a standard deviation for the change from baseline to 10-week outcome in this study of 0.14 logMAR. We will use a two-sided alpha of 0.05, with 90% power to detect difference if the true difference in change from baseline between groups is 0.075 logMAR at 10 weeks. With these assumptions, and accounting for 5% loss to follow-up, we have calculated a necessary total sample size of 158 patients.

A minimum of 158 patients are expected to be enrolled with a goal to enroll an appropriate representation of minorities. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Patients who have signed an informed consent form can be randomized up until the end date, which means the minimum recruitment goal might be exceeded. The maximum number of randomized patients will be 178.

6.5 Interim Analysis and Sample Size Re-estimation

We are unaware of any previous literature reporting on the response to treatment of amblyopia still present after initial treatment with weekend atropine. The sample size estimates above are based on a study of the initial treatment of amblyopia and may not match our definition of no improvement in the current study. Although we feel we have been conservative in our estimate of variation, a sample size re-estimation will be performed once 50% of the originally planned number of patients have completed the trial. A pooled estimate of variance without respect to treatment group will be calculated and used to re-estimate sample size using a procedure that maintains masking.[9] An adjustment will be made to the final alpha based upon this interim sample size re-estimation.

Chapter 7: References

1. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs patching for treatment of moderate amblyopia in children. Arch Ophthalmol 2002;120:268-78.
2. Pediatric Eye Disease Investigator Group. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. Ophthalmology 2004;111:2076-85.
3. Pediatric Eye Disease Investigator Group. Pharmacological plus optical penalization treatment for amblyopia: results of a randomized trial. Arch Ophthalmol 2009;127:22-30.
4. Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with atropine in children: experience of the Amblyopia Treatment Study. Am J Ophthalmol 2003;136:630-9.
5. Brodstein RS, Brodstein DE, Olson RJ, Hunt SC, Williams RR. The treatment of myopia with atropine and bifocals: a long-term prospective study. Ophthalmology 1984;91:1373-9.
6. Kennedy RH, Dyer JA, Kennedy MA, et al. Reducing the progression of myopia with atropine: a long term cohort study of Olmsted County students. Binoc Vis Strabismus Q 2000;15:281-304.
7. Bedrossian RH. The effect of atropine on myopia. Ophthalmology 1979;86:713-7.
8. Chiang MF, Kouzis A, Pointer RW, Repka MX. Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. Binocul Vis Strabismus Q 2001;16:209-15.
9. Gould AL, Shih, W.J. Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. Comm Stat Theory Meth 1992;21:2833-53.