Amblyopia Treatment Study: Vision Therapy

ATS-VT

A Randomized Trial Comparing Patching with Active Vision Therapy to Patching with Control Vision Therapy as Treatment for Amblyopia in Children 7 to <13 Years Old

PROTOCOL

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CHAPTER 1 BACKGROUND & STUDY SYNOPSIS

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG). It is one of a series of randomized trials and observational studies that address management issues related to the treatment of amblyopia in children.

1.1 Study Objective

To compare the effectiveness of patching combined with active vision therapy plus near activities versus patching combined with control vision therapy plus near activities for moderate amblyopia (20/40-20/100) in 7 to <13 year olds.

1.2 Rationale for the Study

Patching and atropine have been traditionally used for the improvement of visual acuity in children with amblyopia. Previous studies have shown that these methods of treatment are effective in young children with functional amblyopia. More recently ATS3[1], a randomized clinical trial of 507 children ages 7-<18, found that part-time patching combined with atropine and near activities improved visual acuity by two or more lines in 53% of the 7 to 12 year olds compared to 25% for optical correction alone. For the 13 to 17 year olds, part-time patching and near activities improved visual acuity by 2 or more lines in 25%, compared to 23% for optical correction alone. While it appears that patching and/or atropine, combined with near activities, can improve visual acuity in some patients ages 7-<18, most patients in the study were left with residual visual acuity deficits. To further improve visual acuity and binocularity in children with amblyopia some eye care providers augment these traditional therapies with vision therapy. Vision therapy is prescribed initially if there is moderate amblyopia with stereopsis. Vision therapy can be added to the treatment regimen once the patient has reached moderate levels of vision loss with stereopsis or if the patient is not responding to the current treatment and still has moderate amblyopia. It is thought that the best candidates for this type of therapy are those children with a minimum level of stereopsis (at least 800") and without constant strabismus. Those children with no stereopsis would not be able to perform the activities in the later stages of therapy utilizing binocular vision.

Vision therapy is a sequence of prescribed activities typically performed on a daily basis at home and weekly in-office, and is directed toward an individual patient's deficient skills. Visual skills are practiced under conditions that provide the patient with feedback. The feedback, along with a gradual increase in the demand of the activities as improvement occurs, enables the patient to improve visual functions such as visual acuity, fixation, accommodation, and vergence skills.

There have been case reports and small sample studies that have shown that vision therapy in combination with spectacles and occlusion is effective in improving the visual acuity of patients with amblyopia.[2-6] Wick et al[4] looked at nineteen patients who were diagnosed with anisometropic amblyopia between the ages of 6 to 49. Seventeen of the patients had moderate amblyopia and two had severe amblyopia, based on the definition of amblyopia used in the Amblyopia Treatment Studies. The patients were treated with a sequence that included spectacle correction, occlusion therapy and both monocular and binocular vision therapy. The outcomes were presented as final visual acuity in the amblyopic eye and the Amblyopia Success Index (ASI), used by Meyer et al.[7] The ASI compares the actual visual acuity result with the maximum improvement of vision. The results are reported as a percent between 0% and 100%. Patients having a result of 0% indicate that they did not have any improvement in final visual

acuity compared to initial acuity. Patients with a result of 100% indicate that their visual acuity reached the maximum level of improvement (20/20) over the course of therapy. Thirteen of the seventeen patients with moderate amblyopia had a final visual acuity of 20/25 or better and all of the patients with moderate amblyopia had 20/30 or better final visual acuity. The mean ASI for the moderate group was 92.67%.

Wick et al. also compared his patients older than ten with the Meyer cohort to see if there was any difference in the ASI between the two groups. Meyer's patients improved an average of 43.7% with constant occlusion and spectacle wear, while Wick's patients improved an average of 92.6% with occlusion (2-5 hours per day), spectacle wear and sequential vision therapy. Wick et al. makes the assessment that the amount of patching is not the determining factor for improvement in visual acuity. They further state that in older patients in order to reach maximum visual acuity spectacle, occlusion and vision therapy are required.[4]

More recent reports on "perceptual learning," an active form of therapy in which amblyopic subjects practice a position-discrimination task, have shown a mean acuity improvement of approximately 30% (two lines) in amblyopic children and adults who had completed occlusion therapy.[8-10] These studies provide support for the notion that the practice of particular visual skills under conditions that provide the patient with feedback (e.g., vision therapy) may be beneficial in improving the visual performance of amblyopic eyes.

The second reason to prescribe active therapy is to enhance or facilitate the effects of occlusion by directly treating the aforementioned deficits found to be associated with amblyopia. Most therapy procedures are designed to remediate specific deficiencies in four main areas: fixation, spatial perception, accommodative efficiency, binocular function and oculomotor control.[5, 11-13]

Lastly, some investigators have suggested that the use of vision therapy may reduce the likelihood of recurrence of the amblyopia.[4, 14] This may be particularly true with anisometropic amblyopia in which vision therapy can be used to improve binocular function.

1.3 Synopsis of Study Design

<u>Major Eligibility Criteria (See section 2.3 for a complete listing)</u>

- Age 7 to <13 years
- Amblyopia associated with anisometropia, strabismus (comitant or incomitant), or both at the time of the eligibility examination
- No constant strabismus at near at the eligibility examination
- Visual acuity in the amblyopic eye between 49 and 71 letters inclusive (20/40 to 20/100 inclusive) on the eETDRS
- Visual acuity in the sound eye of 79 or more letters on the eETDRS (20/25 or better)
- Inter-eye acuity difference of 15 or more letters (3 or more logMAR lines)
- At least 800 seconds of arc on the Randot Preschool Stereoacuity Test
- No previous vision therapy or orthoptics
  - Previous or current amblyopia treatment with spectacles or contact lenses, patching or atropine is permitted
- Single vision spectacles, if needed, worn for at least 16 weeks or until visual acuity documented to be stable, (bifocals not allowed)
- The child has access to a computer on a daily basis (to use the home vision therapy software)

- No other family member is (or has been) enrolled in this study

Treatment Groups

The two treatment regimens for the 16-week treatment period are:

- 2 hours of daily patching combined with 1 hour daily of near activities (that includes 30 minutes of at-home active vision therapy) and weekly in-office active vision therapy
- 2 hours of daily patching combined with 1 hour of daily near activities (that includes 30 minutes of at-home control vision therapy) and weekly in-office control vision therapy

Patients in the study will be randomly assigned to active vision therapy or control vision therapy in a 1:1 ratio. Patients and their parents will be masked to the treatment assignment for the duration of the study.

Spectacle wear will be continued, if prescribed. Patients wearing contact lenses must be willing to switch to spectacles for the duration of the study.

Sample Size

Sample size for this study will be 222 patients.

Visit Schedule

Weekly in-office treatment visits (± 4 days) for 16 weeks and a masked examination at 17 weeks (± 1 week).

At each weekly visit, the patient will be queried regarding diplopia, visual acuity will be measured in each eye, and in-office therapy will be completed. Visual acuity measurements may be completed by a person who is unmasked to the patient's treatment assignment. At the 17-week masked examination the patient will be queried regarding diplopia, and visual acuity, stereopsis, and ocular alignment will be measured. The visual acuity and stereoacuity tests will be performed by a person who is masked to the patient's treatment assignment. Patients also will be asked whether they believe they were receiving active or control vision therapy.

Primary Analysis

The primary outcome measure is the proportion of patients with visual acuity of 20/25 or better in the amblyopic eye at the 17-week masked exam. These patients will be considered treatment responders. The primary analysis will consist of a comparison between the 2 treatment groups of the proportion of treatment responders with adjustment for baseline visual acuity.

Secondary outcomes are stereoacuity at the 17-week masked exam, mean improvement in visual acuity at the 17-week masked exam, and rate of improvement of visual acuity.

Sound eye visual acuity will be reported for each treatment group at the 17-week masked exam as mean change from baseline, distribution of number of lines of change from baseline, and number and proportion of patients losing 2 or more lines from baseline.

Active Vision Therapy Phase for Control Group Non-responders

At the completion of the 17-week visit, the patient and parent will be told their treatment group assignment. Patients in the control group who were not responders will be offered the opportunity to complete a course of active vision therapy that will be identical to what the active group received. Patients will be scheduled for in-office therapy and given the home therapy programs to complete. Parents/patients will have 10 days from the masked examination to

decide whether or not they wish to receive the additional therapy. If they decide within the 10 days, this additional therapy will be paid for by the study. If they decide after the 10 day period, they or their insurance will be required to pay for the vision therapy.

Observation for Recurrence Phase

Active and control group treatment responders will continue in an observation phase for 12 months in order to determine the rate of recidivism once treatment is discontinued. Follow-up visits will occur at 13, 26, and 52 weeks $\pm$2 weeks from the discontinuation of treatment.

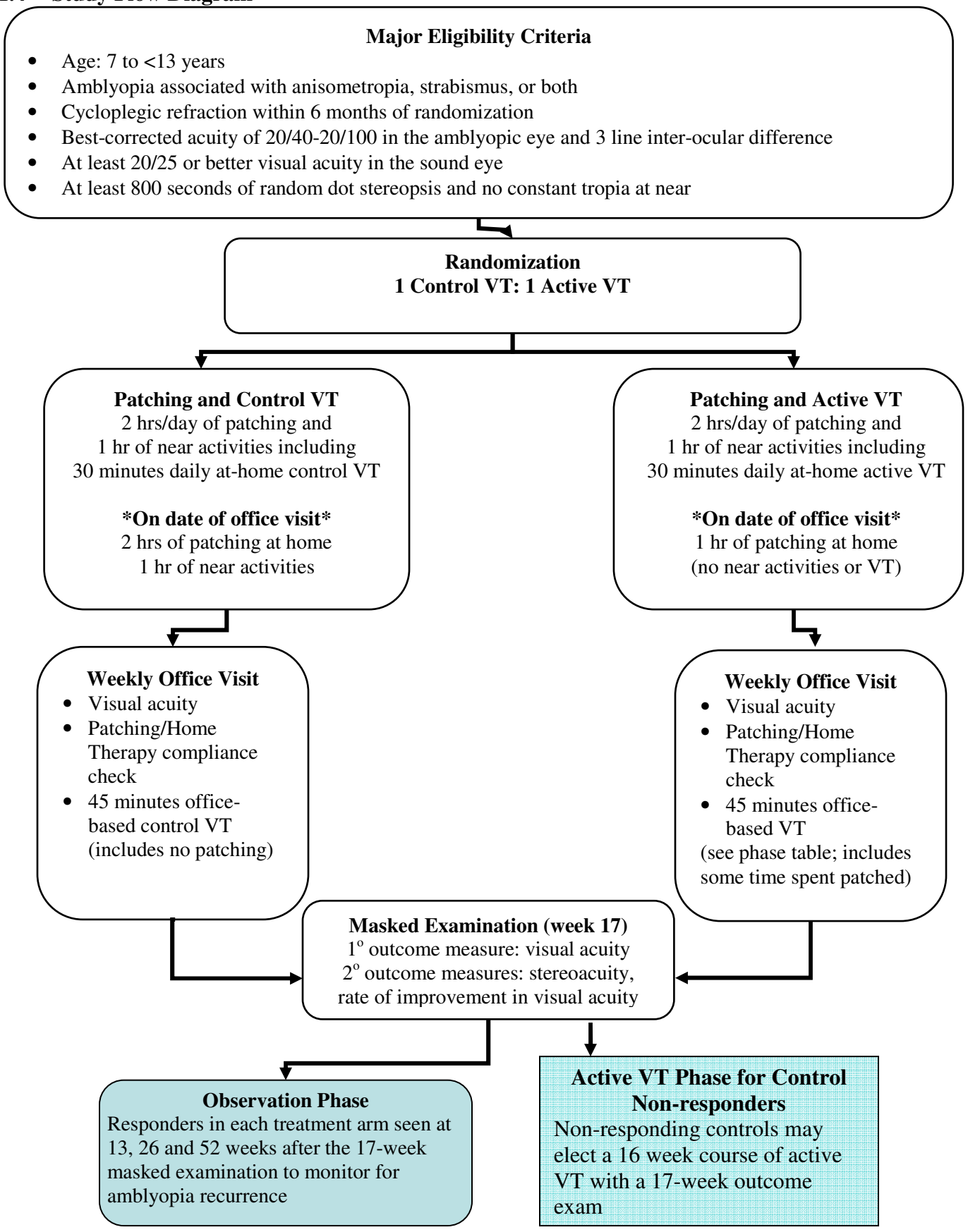
Feasibility Phase

Due to concerns regarding whether sites can recruit a sufficient number of eligible patients, if sites and patients can adhere to weekly office visits, and the high cost of equipment and training for sites, the randomized clinical trial will have an initial feasibility phase. The feasibility phase will consist of seven pre-selected sites, three ophthalmology sites and four optometry sites with demonstrated ability to recruit patients in the desired age group, based on ATS3 performance and documentation of availability of study-eligible patients prior to study initiation. These seven sites will enroll forty-five patients during this initial phase. All patients will be enrolled and treated in full accordance with this protocol. The primary objective of this phase is to determine the feasibility of recruiting the full sample size and successfully completing the randomized clinical trial. To this end, the experience and data collected in this phase will be used to:

1. Determine availability of eligible patients and willingness of parents/patients to be randomized to the proposed treatments.
2. Determine adherence to treatment protocol (i.e., weekly visits), especially in the control group.
3. Test procedures developed to train vision therapists to administer both active and control vision therapies according to protocol. Identify possible problems with training and implementation at the site level.
4. Test feasibility of delivering an office-based vision therapy program for amblyopia in PEDIG sites, particularly the ophthalmology sites.
5. Determine success of masking.
6. To estimate the percentage of patients in the control group who were not classified as responders who elect to undergo a course of active therapy.

In addition, during the feasibility phase, the reasons that eligible patients decline to enroll and that patients are ineligible to be enrolled into the study will be collected. This information will be used to determine whether changes in the protocol for the full scale phase could increase the number of eligible patients or willingness of eligible patients to be enrolled, such as providing computers for at home vision therapy, or increasing payments to families for travel expenses. The decision to continue the study, i.e., add additional sites and recruit the full sample size of 222 patients, will be based on experience and data collected during the feasibility phase of the study.

1.4 Study Flow Diagram



CHAPTER 2 PATIENT ELIGIBILITY AND BASELINE TESTING

2.1 Introduction

Patients are eligible for the study when the criteria in section 2.3 are met and the following are present:

- Investigator intends to prescribe 2 hours of patching per day or patient is being switched to 2 hours of patching per day
- Parent/guardian is willing to bring the patient in for a one hour office visit on a weekly basis for 17 consecutive weeks

Refractive error, if present, must be corrected with glasses before enrollment into the study. Prior correction of refractive error with contact lenses is permitted, but the patient must be switched to spectacles prior to enrollment into the study and wear spectacles for the duration of the study.

2.2 Eligibility Assessment and Informed Consent

A patient is considered for the study after undergoing a routine eye examination (by a study investigator) that identifies amblyopia meeting the eligibility criteria.

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(s). Parent(s) or guardian(s) who express an interest in the study will be given a parent information sheet and a copy of the informed consent form to read. Written informed consent will be obtained from the parent or guardian and the Child Assent Form will be signed by the patient prior to performing any study-specific procedures that are not part of the patient's routine care.

2.3 Eligibility and Exclusion Criteria

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

1. Age 7 to <13 years
2. Amblyopia associated with anisometropia, strabismus (comitant or incomitant), or both*
   a. 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
   b. Criteria for strabismus: At least one of the following criteria must be met:
      - Heterotropia at distance and/or near fixation on examination (with or without spectacles)
      - History of strabismus surgery (or botulinum)
      - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
   c. Criteria for combined mechanism amblyopia: Both of the following criteria must be met:
      - Criteria for strabismus are met (see above)
      - ≥1.00 D difference between eyes in spherical equivalent **OR** ≥1.50 D difference between eyes in astigmatism in any meridian

- *Note: the spherical equivalent requirement differs from that in the definition for refractive/anisometropic amblyopia*

*Additional eligibility criteria apply for patients with strabismus or combined mechanism amblyopia. See criterion 3 below.

3. No constant strabismus at near
   - If constant strabismus of any measurable degree is present at near during the eligibility examination, the patient is not eligible.
   - Patients who have a history of constant strabismus at near prior to the eligibility examination, but have intermittent strabismus at near at the eligibility examination are eligible for the study, provided they meet all other eligibility criteria.
   - Patients with constant strabismus at distance with intermittent or no strabismus at near are eligible for the study, provided they meet all other eligibility criteria.
4. Visual acuity, measured using the eETDRS protocol on the Electronic Visual Acuity Tester (EVA) *(the protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual)*, meeting the following criteria:
   - Best-corrected visual acuity in the amblyopic eye between 49 and 71 letters inclusive (20/40 to 20/100 inclusive)
   - Best-corrected visual acuity in the sound eye 79 or more letters ($\geq$20/25)
   - Inter-eye acuity difference 15 or more letters ($\geq$3 logMAR lines) (i.e., amblyopic eye acuity at least 3 lines worse than sound eye acuity)
5. Spectacle correction for measurement of enrollment visual acuity must meet the following criteria and be based on a cycloplegic refraction (using cyclopentolate 1%) that is no more than 6 months prior to enrollment:
   a. Requirements for spectacle correction:
      - Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
      - Hypermetropia must not be undercorrected by more than +1.50 D spherical equivalent, and reduction in sphere must be symmetric in the two eyes
      - 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
      - Myopia of amblyopic eye greater than 0.50 D by spherical equivalent must be corrected, and the glasses must not undercorrect the myopia by more than 0.25 D or overcorrect it by more than 0.50 D.

   b. Spectacles meeting above criteria must be worn either:
      1) For 16 weeks immediately prior to enrollment/randomization, 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 1 logMAR 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) by having the patient return in new glasses for the first measurement. The second acuity measure does not have to be made through the same prescription as the first, if the second measure is made through a more accurate prescription. *Note: because this determination is a pre-study procedure, the method of measuring visual acuity is not mandated, although eETDRS testing is preferred if done as part of usual care.*

- Prior contact lens wear is permitted, but patients must be willing to switch to spectacles for the duration of the study. Stability of visual acuity in spectacles according to above criteria must be documented prior to enrollment.
- Prior bifocal wear is permitted but patient must switch to and show stability with single vision glasses before being enrolled in the study. There can be no constant strabismus at near without the bifocals.

6. Near stereoacuity of 800 seconds of arc or better on the Randot Preschool Stereoacuity test
7. No previous home-based, office-based or computerized vision therapy or orthoptics
8. Previous or current amblyopia treatment with spectacles, contact lenses, patching, or atropine is permitted. At the time of enrollment the patient must be:
   - currently patching for 2 hours per day, *or*
   - ready to be switched to 2 hours per day of patching from another patching dose or from atropine, *or*
   - not currently on treatment (other than spectacles or contact lenses) and ready to initiate patching for 2 hours per day.

   The decision whether the patient is a suitable candidate to be switched to 2 hours per day of patching is at investigator discretion. Atropine treatment must be discontinued at least 2 weeks prior to enrollment. Patients taking atropine may be switched to patching when atropine is discontinued and enrolled 2 weeks later, if the investigator does not wish to stop amblyopia for 2 weeks. All patients, regardless of prior treatment status, must meet all other eligibility criteria at the time of enrollment.
9. No known skin reactions to patch or bandage adhesives
10. Cycloplegic refraction within 6 months prior to enrollment
11. Ocular exam within 6 months prior to enrollment revealing no ocular cause for reduced visual acuity
12. No developmental disability, mental retardation, or learning disability diagnosis that in the investigator's judgment would interfere with treatment.
13. Children with attention deficit hyperactivity disorder (ADHD) may be enrolled if the investigator feels that the patient could still properly perform the therapy activities.
14. No myopia more than -6.00 D spherical equivalent in the amblyopic eye
15. No prior intraocular or refractive surgery
16. Parent does not anticipate relocation outside area of active VT Study site within the next 5 months
17. Patient and parent are willing to accept randomization and be available for 17 consecutive weeks of office visits and follow up
18. Siblings of patients already enrolled in this study, and children of ophthalmologists, optometrists, orthoptists, and vision therapists are excluded.
19. Patients must have access to a computer on a daily basis.

2.4 Examination Procedures

2.4.1 Historical Information

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

2.4.2 Clinical Testing for Enrollment

1. Visual acuity in each eye (right eye first) is measured by the ATS single-surround eETDRS testing protocol on the Electronic Visual Acuity Tester. The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual. Aspects of the testing protocol that are specific to this study are indicated below:
   - Testing must be done without cycloplegia (with spectacles, if worn) no more than 7 days prior to randomization.
   - Because 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.
   - 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. Ocular motility examination
   - Measurement of predominant alignment by Simultaneous Prism and Cover Test (SPCT) in primary position at distance and near.
   - Testing must be done without cycloplegia (with spectacles if worn) no more than 7 days prior to randomization
3. Ocular examination as per investigator's clinical routine to rule out a cause for reduced visual acuity other than amblyopia
   - ➢ if performed within prior 6 months, does not need to be repeated at time of enrollment.
4. Binocularity testing (without cycloplegia): Titmus Fly and Randot Preschool Stereoacuity test
5. Cycloplegic refraction using cyclopentolate 1% as per investigator's usual routine
   - ➢ if performed within prior 6 months, do not need to repeat at time of enrollment

2.5 Randomization of Eligible Patients

Assuming that visual acuity in the amblyopic eye on the better of the initial or repeat tests is 20/40 to 20/100, inclusive, and acuity in the sound eye is 20/25 or better, the patient will be randomly assigned with 1:1 probability to either (1) the Active Treatment group or (2) the Control group.

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

Once a patient is randomized, that patient is included in the study and in all analyses regardless of whether the assigned treatment is received. Thus, the investigator must not randomize a patient until he/she is convinced that the parent/guardian will accept either of the treatment regimens.

Initial therapy visit must be scheduled within 10 days of the randomization visit.

CHAPTER 3 TREATMENT

3.1 Randomization Groups

Each patient will be randomly assigned to one of two treatment groups in a 1:1 ratio:

1. Two (2) hours of daily patching combined with 30 minutes of daily near activities at home, 30 minutes of daily at-home active vision therapy, and a weekly 45 minute in-office active vision therapy session.
2. Two (2) hours of daily patching combined with 30 minutes of daily near activities at home, 30 minutes of daily at-home control vision therapy, and a weekly 45 minute in-office control vision therapy session.

Spectacle wear will be continued if prescribed. Patients wearing contact lenses must be switched to spectacles prior to enrollment for the duration of the study.

Weekly Office Visits: Each patient randomized into the study will be seen on a weekly basis for administration of treatment for 16 weeks. At each office visit, the patient will be queried regarding diplopia and visual acuity in each eye will be measured using the eETDRS protocol. Each group will receive 45 minutes of vision therapy activities dependent upon their group assignment.

Daily patching and at-home vision therapy will be continued through the 17 week masked examination.

3.1.1 Measurement of Visual Acuity

Prior to each in-office therapy session the vision therapist (or other ATS certified visual acuity tester) will measure the visual acuity of each eye using the eETDRS protocol *(the protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual)*. The person completing the visual acuity measurement for in-office therapy sessions will not be required to be masked to the patient's treatment assignment.

3.1.2 Sequencing of In-Office Active Vision Therapy

There are three categories of active vision therapy activities. The instructions to the therapist for all therapy procedures will be specified in the Manual of Procedures. These instructions will include a list of specific goals which should be met for each procedure before a patient can proceed from one phase to the next. The three categories of therapy are:

- Accommodation
- Anti-Suppression
- Vergence

The amount of time the patient wears a patch during the in-office therapy session will be dependent upon the category and phase of therapy he/she is performing at the weekly office visit.

3.1.3 At-Home Vision Therapy for Active Group

The patients randomized to the active arm of the study will also perform 30 minutes of regimented vision therapy and 30 minutes of near activities. This home therapy will be completely computer based. The two programs that will be assigned to the patients in this group are the Home Therapy System and the Amblyopia iNet Program.

The Home Therapy System program will have therapy for vergence. The Amblyopia iNet Program will include activities for eye-hand coordination, tracking, and visual discrimination. Home VT is performed while wearing the patch. The exception to this is when the patient is using the HTS software, which is performed without the patch. See section 3.2 for further discussion on near activities.

3.1.4 In-Office Control Vision Therapy

The control vision therapy will be structured based on weekly schedules. Each week patients will perform the control therapy procedures as described in the Manual of Procedures.

During the control vision therapy sessions the patient will not wear a patch. (Note: the control vision therapy patients will be instructed to patch for 2 hours and perform 1 hour of near activities while patched at home on the day of the office visit. Active vision therapy patients will be instructed to patch for 1 hour at home and perform no near activities or vision therapy in order to have similar amounts of patching times between the groups.)

3.1.5 At-Home Control Vision Therapy

Patients in the control group will be assigned 1 hour of near activities each day which will include 30 minutes of computer activity with the study specific computer program. These activities will be performed while patients are wearing their patches. See section 3.2 for further discussion on types of near activities, and the Manual of Procedures for further detail on the at-home computer activities and study specific computer program.

3.1.6 Reporting of Information About Therapy Sessions

After each therapy session, the site will complete a checklist specifying the therapy completed.

3.1.7 Initial In-Office Therapy Visit

The initial in-office therapy visit must be scheduled within 10 days of randomization. Scheduling on the day of randomization is permitted.

Study treatment commences on the day of the first in-office vision therapy session. At the end of the session, patches and the at-home vision therapy software should be given to the patient. The patient and parent are instructed in their use and given a copy of the treatment instruction sheet. They are also given a calendar on which to record the amount of time spent patching and using the home VT software each day.

Patients in the active group should be instructed to patch 1 hour that day. No near activities or home VT are completed that day. This is the same as other days on which an in-office therapy visit is completed.

Patients in the control group should be instructed to patch 2 hours that day and perform 1 hour of near activities while patched. No (control) home VT is completed that day. This is the same as other days on which an in-office visit is completed.

Both treatment groups are instructed to patch 2 hours and perform 1 hour of near activities of which ½ hour should be spent using the at-home VT software (either active or control software) starting the day after the 1st in-office treatment visit.

3.2 Patching and Near Activities on Days When an Office Visit is NOT Scheduled

Each patient, regardless of treatment assignment, is prescribed 2 hours of daily patching at home combined with 1 hour of near activities (including 30 minutes of home-based active or control

vision therapy according to treatment group) on days when an office visit is not scheduled. The prescription of 2 hours daily patching at home must be continued through the 17 week masked examination. No increase in amount of daily patching is permitted.

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 prescribed, then plano glasses will be provided.

The following instructions will be given to the parent:

- The 2 hours of patching should be continuous.
- If the child falls asleep while wearing the patch, this time should not be counted as patching time.

Near activity tasks may include any of the following activities:

- Crafts, coloring, tracing, cutting out objects, dot-to-dot connecting, 'fill in the symbols', 'symbol sequence', or other activities requiring eye-hand coordination
- Hidden pictures and word finds
- Video games (e.g. Game Boy)
- Computer/internet
- Written homework
- Reading
- Building models, knitting, stringing beads

Accommodative therapy with ophthalmic lenses may NOT be performed as a "near activity."

A list of these activities will be given to the parents of children enrolled in both treatment groups.

In addition to these general near activities, patients in the active and control vision therapy group will be assigned 30 minutes of at-home vision therapy. These 30 minutes will be included in the requirement for 1 hour of near activities to be completed while patched. The protocol for at-home vision therapy is specified in the Manual of Procedures.

3.2.1 Patching and Near Activities at Home on the Day of the Weekly In-Office Session

In order to equalize patching time between the two groups the following changes to the patching schedule will be made on the days of an in-office visit:

- Active Vision Therapy Group: After the weekly in-office vision therapy session the child will be instructed to wear the patch for only 1 hour at home that day and not to do any of the near activities (this includes not doing the at-home computer activities). The child will return to his/her normal schedule the next day.

- Control Vision Therapy Group: After the weekly in-office control session the child will be instructed to wear the patch for 2 hours with 1 hour of near activities as usual. The child will be instructed to skip the at-home computer activities that day. The child will return to his/her normal schedule the next day.

3.3 Home Calendar Logs

Parents will record the amount of time the patient wore the patch at home each day.

The calendars will be brought to the weekly office visits and a summary of the data will be entered onto the study website, along with other data collected at therapy visits.

At each visit, the logs will be reviewed by the therapist and an assessment of patching compliance recorded on the Follow-up Examination Form.

CHAPTER 4 FOLLOW-UP EXAMINATIONS

4.1 Follow-up Schedule

All patients will have the following study visits:

- Weekly office visits ± 4 days for 16 weeks for administration of in-office vision therapy
- 17-week masked outcome visit ± 1 week

4.2 Testing Procedures

4.2.1 Weekly In-Office Vision Therapy Visits

The following activities/testing will be performed at the weekly office visits in the specified order:

- Binocular diplopia query
  - If a patient reports the onset of constant diplopia, treatment will be discontinued. If diplopia has resolved at the next week's office visit, therapy will be reinstituted; however, anti-suppression therapy will not be performed for those assigned to Active vision therapy
- Measurement of visual acuity in each eye by the eETDRS testing protocol on the Electronic Visual Acuity Tester
  - The right eye is tested first, then the left eye
  - Testing is performed without cycloplegia with spectacles (if worn)
- In-Office Vision Therapy
  - Active or Control vision therapy based on randomization
- Completion of the therapy progress checklist

All patients will continue to have weekly in-office treatment sessions even if the visual acuity reaches 20/20 during the study.

All procedures at weekly vision therapy visits are permitted to be performed by a person who is unmasked to the patient's treatment assignment.

4.2.2 Scheduling of Weekly In-Office Vision Therapy Visits

Ideally, treatment visits should be exactly 7 days apart; however, this will not always be possible. As such, we have established acceptable visit windows for the time between each in-office vision therapy visit. The acceptable window for each appointment is +/- 4 days from the original targeted date (as calculated from the initial therapy session). Furthermore, no more than two appointments can be scheduled within a 7 day period and successive appointments must be more than 2 days apart.

Coordinators and Vision Therapists should consider creating a standing appointment time for each patient during the study. Care should be given to not schedule study patients back to back if possible to help minimize potential interaction between patients in different treatment arms.

4.2.3 17-Week Masked Examination

The following procedures will be performed at the 17-week Masked Outcome Examination. The visual acuity and stereoacuity tests need to be performed by a masked examiner. The order of procedures will be:

1. Binocular diplopia query

2. Measurement of visual acuity in each eye by the eETDRS testing protocol on the Electronic Visual Acuity Tester. (Must be performed by a masked examiner. The right eye is tested first.)
3. Titmus Fly and Randot Preschool Stereoacuity Test (Must be performed by a masked examiner.)
4. Ocular alignment by SPCT
5. Ask the patient and the parent/guardian if they believe they were receiving active vision therapy or control therapy
    - This must be the last item completed.

4.2.4 Unmasking of treatment assignment

At the completion of the 17-week visit, the patient and parent will be told their treatment group assignment. Patients in the control group will be offered the opportunity to complete a course of active vision therapy that will be paid for by the study. To be paid by the study the parents/patient must decide to enroll in the vision therapy within 10 days after the completion of the 17-week masked examination.

CHAPTER 5 OBSERVATION FOR RECURRENCE

5.1 Overview

Active Treatment Group and Control Treatment Group responders in the randomized trial are continued in an observation phase for 12 months in order to determine the rate of recidivism following successful treatment after treatment is discontinued.

Treatment group responders are patients who improved to 20/25 or better in the amblyopic eye and maintained or improved the visual acuity in the non-amblyopic eye on treatment, and for whom the investigator is ready to discontinue all treatment other than spectacles (if prescribed) at the 17-week visit.

5.2 Visit Schedule

Follow-up visits will occur at 13, 26, and 52 weeks $\pm$ 2 weeks timed from the discontinuation of treatment. Additional visits are at the discretion of the investigator.

5.3 Examination Procedures

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

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

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

- Measurement of ocular deviation in primary position at distance and near by Simultaneous Prism and Cover Test (SPCT)
- Binocularity testing (Titmus Fly and Randot Preschool Test)

5.4 Recurrences of Amblyopia

Definition of Recurrence

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

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

5.5 Treatment of Amblyopia Recurrence

If amblyopia recurs and meets the study's recurrence criteria, the investigator may institute any form of amblyopia therapy, which will be recorded on the follow-up exam form. If an

investigator believes that treatment should be reinstituted but the patient has not met the study's recurrence criteria, a Protocol Chair should be contacted to discuss the case.

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

CHAPTER 6 CONTROL NON-RESPONDERS ELECTING ACTIVE VISION THERAPY

6.1 Overview

Patients in the control treatment group who are classified as a non-responder at the 17-week masked outcome examination will be offered a course of active vision therapy. If the patient/parents elect the additional therapy within 10 days after the completion of the 17-week masked examination they will follow the same course of treatment as the active group. During this additional treatment they will be considered to be in the study and the therapy will be paid for by the study. An outcome examination mirroring the 17-week masked examination will be performed at the completion of active therapy.

The goal of this phase is to estimate the proportion of control patients who meet criteria for treatment success at the end of the course of active therapy. Although it will not be possible to attribute improvement to active therapy versus increased time on patch, this will allow an assessment of what proportion of patients benefit from increased time on treatment that includes vision therapy.

6.2 Start of Additional Therapy

Once patients elect to undergo the additional treatment they will be required to begin the active therapy within 21 days after the primary outcome examination.

6.3 Weekly In-Office Vision Therapy Visits

The following activities/testing will be performed at the weekly office visits in the specified order:

- Binocular diplopia query
- If a patient reports the onset of constant diplopia, treatment will be discontinued. If diplopia has resolved at the next week's office visit, therapy will be reinstituted; however, anti-suppression therapy will not be performed during the rest of the therapy
- Measurement of visual acuity in each eye by the eETDRS testing protocol on the Electronic Visual Acuity Tester (performed only at the 7 and 8 week treatment visits)
  - The right eye is tested first, then the left eye
  - Testing is performed without cycloplegia with spectacles (if worn)
- In-Office Vision Therapy
  - Active vision therapy will be completed each week. The therapist will follow the Manual of Procedures for the Active Vision Therapy.
- Completion of the therapy progress checklist

All patients will continue to have weekly in-office treatment sessions even if the visual acuity reaches 20/20 during the study.

All procedures at weekly vision therapy visits are permitted to be performed by a person who is unmasked to the patient's treatment assignment.

6.4 Scheduling of Weekly In-Office Vision Therapy Visits

Ideally, treatment visits should be exactly 7 days apart; however, this will not always be possible. As such, we have established acceptable visit windows for the time between each in-office vision

therapy visit. The acceptable window for each appointment is +/-4 days from the original targeted date (as calculated from the initial therapy session). Furthermore, no more than two appointments can be scheduled within a 7 day period and successive appointments must be more than 2 days apart.

Coordinators and Vision Therapists should consider creating a standing appointment time for each patient during the study. Care should be given to not schedule study patients back to back if possible to help minimize potential interaction between patients in different treatment arms.

6.5 17-Week Outcome Examination

The following procedures will be performed at a 17-week Outcome Examination. The order of procedures will be:

1. Binocular diplopia query
2. Measurement of visual acuity in each eye by the eETDRS testing protocol on the Electronic Visual Acuity Tester. (The right eye is tested first.)
3. Titmus Fly and Randot Preschool Stereoacuity Test
4. Ocular alignment by SPCT

The examiner need not be masked to the treatment.

CHAPTER 7 MISCELLANEOUS CONSIDERATIONS

7.1 Patient Withdrawals

A patient (and in this case the parent 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 similarity of study procedures to routine clinical practice. If the parent or guardian indicates that he/she wants to withdraw the child from the study, the investigator personally should attempt to speak with him/her to determine the reason.

7.2 Risks

There are no risks involved in this study that would not be part of usual care. The risks involved in this study are identical to those for patients treated with the study treatments who do not participate in the study.

7.2.1 Risk of Patching

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

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

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

Patching could precipitate the development of a manifest ocular deviation. If treatment precipitates the development of a strabismus (e.g., esotropia in child with hyperopia), the parent will be advised to have the patient see the investigator as soon as possible. The decision to continue or discontinue therapy will be left to the discretion of the investigator and parent. If the decision is made to continue treatment, the patient will remain in their assigned group.

There are some activities that should not be performed when patched due to the level of vision in the amblyopic eye and some reduction in visual field. These activities include riding a bike, in-line skating, skateboarding, or other activities in which the child could get hurt. The consent form will explicitly instruct parents not to allow their child to perform such activities while patched.

7.2.2 Risk of Examination Procedures

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

7.2.3 Diplopia

Amblyopia therapy could induce diplopia through occlusion of the dominant eye and disruption of habitual suppression of the non-dominant eye during binocular conditions. In a study of 404 patients in this age group using patching and atropine eye drops, but without vision therapy, there were no cases of permanent constant diplopia. Four patients not reporting diplopia at the outset reported it during follow up, with 3 resolving by the last visit and 1 reporting it intermittently.[1] Although rare, it is possible that the diplopia could persist even after treatment is discontinued. Data on the frequency of this complication will be collected as part of the study.

7.2.4 Intercurrent Events

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

2. Eye injuries or the development of an eye problem that might affect vision will be reported on the Follow-up Examination Form. Likewise, the development of a serious medical problem that might affect the patient's study participation will be recorded.

3. Patients developing a new, constant tropia should continue on their assigned treatment. The therapist will eliminate elements of the therapy that would be inappropriate for a child with constant tropia. However, these patients are still considered as enrolled in the study and included in the primary outcome analysis. Thus, every attempt should be make to complete the masked outcome assessment at 17 weeks. Investigators should contact a protocol chair to discuss these cases as they arise.

7.3 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 or her IRB.

7.4 Patient Payments

Patient payments include a $5 gift certificate given to the child at the end of each weekly office visit, and monthly check for $20 for each completed in-office visit to defray travel costs to be issued to the parent. If there are extenuating circumstances, and the patient is unable to complete study visits without additional funds due to travel costs, additional funds may be provided.

7.5 Discontinuation of Study

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

7.6 Contacts by the Jaeb Center for Health Research (JCHR)

The JCHR serves as the PEDIG Coordinating Center (CC). The CC will be provided with the parent/guardian's contact information. The CC staff may contact the parent/guardian during the study to answer any questions and discuss any problems during the study. Permission for such contacts will be included in the Informed Consent Form. A patient newsletter, study updates,

and a study logo item may be sent. Patients will be provided with a summary of study results in a newsletter format after completion of the study by all patients.

CHAPTER 8 SAMPLE SIZE AND STATISTICAL ANALYSIS

The estimation of sample size and the statistical analysis plan are summarized below and detailed in separate documents. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan, which will supersede this section when it is finalized.

8.1 Sample Size Estimation

The sample size estimate was computed based on a Fisher's exact test comparing proportions of patients in each treatment group with 20/25 or better visual acuity at the 17-week masked exam. Patients meeting this criterion will be considered a treatment success. Based on data from ATS3 patients meeting eligibility criteria for the ATS-VT study, it is estimated that 30% of patients in the control vision therapy group will have 20/25 or better visual acuity at the 17-week masked exam. To detect an absolute increase of 20% in the active vision therapy group to an outcome proportion of 50% with type I error of 5% (one-sided) and power of 90%, a total of 222 patients is needed. Patients who drop out of the study prior to completion of the 17 week masked exam will be counted as treatment failures in the primary outcome analysis; hence, no adjustment to the sample size has been made for dropouts.

A one-sided alpha is used as there is interest in testing only whether the outcome proportion for active vision therapy is significantly higher than for controls. If not higher, then there is no reason to use active vision therapy in clinical practice. An absolute increase in outcome proportion of 20% was chosen as the smallest improvement for which clinicians would be willing to use vision therapy in their clinical practice, given the time commitment and extra expense demanded of patients.

Counting dropouts as treatment failures may lower the expected proportion with treatment success in both treatment groups. In this case, the power for the primary outcome comparison is increased to greater than 90%. Adjustment for baseline visual acuity in the primary analysis also would be expected to improve statistical power.

Feasibility phase sample size

A feasibility phase sample size of 45 patients is judged sufficient to meet feasibility phase goals as specified in section 1.3. It is anticipated that there will be 7 clinical sites with each site expected to enroll 6-7 patients. No site will be permitted to enroll more than 10 patients. The sites participating in the feasibility phase will be selected on the basis of ability to enroll children in the desired age range and will provide an upper limit for likely monthly recruitment per site in the full-scale study.

Observation phase sample size

Based on the responder rates assumed for the trial sample size calculation, it is expected that 111 x 0.30=33 patients from the control group and 111 x 0.50=56 patients from the active VT group will be eligible for the observation phase, for a total of 89 patients. However, patients who drop out of the trial prior to completion will not be available for enrollment into the observation phase, and additional patients may drop out during the observation phase. Assuming that 20% of observation phase-eligible patients drop out at any stage of the trial, about 70 patients will have complete observation phase data; of these, 44 will be from the active VT group and 26 from the control group.

The primary goal of this phase will be to estimate the proportion of patients with recurrence of amblyopia (as defined in protocol section 5.1.4) during the 1 year observation phase. Based on data from ATS3, the expected proportion with recurrence in the control group is 7%. If the recurrence in the VT study is similar, the expected width of the 95% confidence interval on the recurrence proportion will be ±8% for the active VT group, ±11% for the control group, and ±7% for both groups combined.

Sample size for Active VT phase for non-responding controls

Patients in the control group who have not met the criterion for treatment success at the 17 week masked exam will be offered a 16 week course of active VT treatment free of charge. After the 16 weeks of treatment, these patients will have an outcome exam that mirrors the 17-week RCT outcome exam. The goal of this phase is to obtain an estimate of the proportion of control patients who meet criteria for treatment success at this second outcome exam following a course of active VT treatment.

It is estimated that about ½ of patients who are eligible for this phase of the study will elect to participate; this corresponds to 40 patients. With this sample size, the expected ½ width of the 95% confidence interval on the proportion of treatment success is approximately ±10%, assuming an underlying success proportion of 10%.

8.2 Primary Outcome Analysis

The primary analysis will consist of a comparison of proportions of patients in the two treatment groups who have 20/25 or better visual acuity at the 17-week outcome exam, with adjustment for baseline visual acuity, using logistic regression. The primary analysis will follow the 'intent-to-treat' principle in which patients are analyzed according to randomized treatment assignment, regardless of whether the treatment was actually received or completed. Dropouts will be counted as treatment failures in the primary analysis.

A secondary analysis that counts study dropouts as treatment successes will be performed. The true treatment effect must be bracketed within the estimated treatment difference obtained in the primary analysis and this secondary analysis. If these are within 10% of each other using the absolute difference, the primary analysis will be considered the definitive analysis. Otherwise, both estimates will be included in the publication of study results along with a discussion of the implications for study conclusions and patient management.

A secondary analysis that estimates the treatment difference based on study completers only also will be performed.

The treatment effect in subgroups based on baseline factors will be assessed in preplanned secondary analyses of the primary outcome. The subgroups of interest will be those based on baseline amblyopic eye visual acuity, age, baseline stereoacuity, prior treatment, practice type (ophthalmology or optometry), and treatment compliance (excellent/good or fair/poor). In accordance with NIH guidelines, estimates of treatment effect by gender and race/ethnicity also will be computed.

8.3 Safety Analysis

Safety data consisting of the number and proportion of patients in each treatment group experiencing the following events will be compiled and included in all reports to the DSMC:

- Loss of 2 or more lines in sound eye visual acuity from baseline to the 17-week masked exam
- Development of diplopia at any time during treatment and whether it has resolved by the 17-week masked exam
- Development of a new ocular deviation and whether it has resolved by the 17-week masked exam

8.4 Interim Analysis

An analysis of primary outcome data, secondary outcome data, and safety data will be provided to the DSMC twice each year. A formal statistical plan for interim monitoring of primary outcome data will be developed in conjunction with the DSMC.

8.5 Observation Phase Analysis

The primary analysis of observation phase data will consist of estimation of the proportion (and 95% confidence interval) of patients with recurrence of amblyopia (as defined in section 5.1.4) during the observation phase using the Kaplan-Meier method. Additionally, a separate estimate and 95% confidence interval for each treatment group also will be obtained.

8.6 Analysis of active VT phase for non-responding controls

The primary analysis of data from this phase will consist of estimation of the proportion and 95% confidence interval of patients with treatment success using the exact binomial method. As for the primary outcome analysis of the RCT, dropouts during the course of active treatment will be considered as treatment failures.

8.7 Secondary Outcome Analyses

8.7.1 Mean improvement in visual acuity

A secondary analysis consisting of a treatment group comparison of logMAR visual acuity scores in the amblyopic eye obtained at the 17-week masked exam, adjusted for baseline visual acuity score, will be performed using analysis of covariance (ANCOVA).

8.7.2 Determination of rate of visual acuity improvement

Determination of the rate of visual acuity improvement in study patients will be based on all visual acuity measurements from the weekly visits, including the baseline and 17-week masked exam. Using all available visual acuity measurements, a linear slope of visual acuity over time will be computed for each patient and compared between treatment groups using linear mixed models methodology. If, based on inspection of individual plots of visual acuity over time and average visual acuity over time by treatment group, it appears that the time course of visual acuity improvement is not linear, 2 linear slopes of visual acuity over time will be computed for each patient. The first slope will be based on visual acuity measurements from baseline through week 8, and the second will based on visual acuity measurements from week 9 through week 17. Again, these 2 slopes will be compared between treatment groups using linear mixed models methodology. The latter analysis will allow for the possibility that overall visual acuity at 17 weeks does not differ between the 2 treatment groups, but that one treatment achieves endpoint visual acuity sooner than the other.

8.7.3 Stereoacuity

Distribution of stereoacuity at the 17-week outcome exam and change in number of categories of stereoacuity from baseline to the 17-week masked exam will be compared between treatment groups using the exact Wilcoxon rank sum test.

8.8 Feasibility Phase Analysis

The feasibility phase is not powered to be able to detect a difference between treatments in effectiveness. Active vision therapy would need to have greater than 80% effectiveness with respect to the primary visual acuity endpoint for a treatment difference to have a reasonable chance of being detectable with a sample size of 45, a highly unlikely possibility. Hence, no statistical testing will be conducted. Rather, the primary goal of data analysis will be descriptive in nature, and intended to aid in the evaluation of study feasibility and adherence with treatment protocol. This will include:

- Estimation of recruitment rate (overall and by center);
- Estimation of recruitment rate by prior treatment status;
- Enumeration and review of cases, if any, of ineligible patients enrolled;
- Estimation of the percentage of patients missing the treatment visit for each treatment visit (overall, and by treatment);
- Distribution of number of treatment visits missed per patient (overall, by treatment group, and by site)
- Estimation of mean and range for number of non-office visit days the home computer therapy was used (by treatment group);
- Summary of patient progress through treatment protocol (number and percent of patients in each phase by week of treatment and treatment assignment);
- Identification and review of patients making insufficient or very rapid progress with treatment (patients appearing as outliers in the above table);
- Enumeration and review of all cases, if any, with adverse events (diplopia, reverse amblyopia, development of a new ocular deviation);
- Estimation of retention and dropout rates of enrolled patients at 17 weeks (overall and by center);
- Estimation of percentage of patients with valid outcome data for each outcome at 17 weeks (overall and by center);
- Estimation of the percentage of patients in each treatment group who correctly and incorrectly identify their treatment group assignment;
- Estimation of the percentage of patients in the control group not classified as treatment responders who elect to undergo a course of active therapy.

Patients will be classified into 3 groups according to prior treatment status for the purpose of estimating recruitment rate within each of the groups. These 3 groups are:

- Patients who were not treated for amblyopia within 6 months prior to enrollment;
- Patients who were treated within the past 6 months who initially had severe amblyopia and were enrolled in the study after improvement to moderate amblyopia; and
- All other patients who were treated within the past 6 months.

The purpose of this stratification is to determine which, if any, of these groups has sufficient numbers of patients that they could be targeted for a full-scale trial of vision therapy.

Outcome data consist of data from the testing procedures at the 17-week examination as specified in section 4.2.2., and visual acuity data collected at the weekly treatment visits. For the purposes of the feasibility assessment, to be considered valid, outcome data must be collected according to study protocol-specified procedures and within the designated time window for the visit.

Guidelines for judging successful completion of the feasibility phase with respect to the above criteria are specified in a separate document (Sample Size Estimation and Statistical Analysis Plan).

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