AMBLYOPIA TREATMENT STUDY (ATS18)

Study of Binocular Computer Activities for Treatment of Amblyopia

PROTOCOL

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CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and is funded through a cooperative agreement from the National Eye Institute.

1.1 Background

Epidemiology & clinical characteristics

Amblyopia is the most common cause of reduced monocular visual acuity in children and young adults, with estimates of prevalence ranging from 1% to 5%.[1, 2] The most common associated amblyogenic risk factors are uncorrected anisometropia, strabismus, or a combination of these. In addition to reduced visual acuity, amblyopic subjects may also have dysfunctions of accommodation, fixation, binocularity, vergence, reading fluency, and contrast sensitivity.[3-10]

Treatment –current methods and outcomes

The current mainstay of amblyopia treatment is spectacle correction (when there is uncorrected refractive error) followed by part-time patching or atropine penalization of the fellow eye.[11-15] Randomized clinical trials and prospective observational studies have shown improvement in visual acuity with spectacles, patching, and atropine treatment, even in older children where treatment has historically not been performed.

In younger children, age 3 to <7 years, although current treatments with part-time occlusion and atropine drops are somewhat effective,[11-15] residual amblyopia (20/32 or worse) is still present in 54% of children at age 10 years[16] and 40% at age 15 years.[17]

In older children, age 7 to 12 years, current treatments are even less effective. The majority of older children still have residual amblyopia after treatment;[18-20] in 7- to 12-year-old children, 80% treated with atropine and 74% treated with patching had residual amblyopia of 20/32 or worse.[18]

In teenagers, aged 13 to 17 years, there is only limited evidence that patching is even minimally effective. In a previous PEDIG study, 23% of children randomly assigned to optical treatment alone responded (≥0.2 logMAR improvement) vs 25% in those who received both optical treatment and part-time patching.[20] Effectiveness of patching was somewhat better in those teenagers who had not previously been treated; 47% responded to patching with optical treatment versus 20% to optical treatment alone, but even so, the majority did not respond to patching.[20]

One possible reason for failure of part-time patching treatment in some younger children and many older children is poor compliance with the prescribed treatment regimens.[21, 22] Nevertheless, data from studies using an occlusion dose monitor[23, 24] suggest that many children do successfully comply with prescribed part-time patching treatment and yet fail to respond to treatment, suggesting that part-time patching is ineffective for treating amblyopia in some children.

In addition, patching has negative psychosocial effects for many children, and children often resist wearing a patch. Some children and their parents rate patching poorly from the standpoint of adverse effects of treatment, treatment compliance, and social stigma.[25, 26]

Based on the prevalence of residual amblyopia with current part-time patching treatment and the challenges of compliance with patching, new treatments for amblyopia are needed, particularly those that can be visually unobtrusive and that do not overtly interfere with the vision of the fellow eye.

Binocular treatment

Although the predominant approach for amblyopia treatment is monocular penalization by patching, atropine, or a Bangerter filter, some investigators have advocated a binocular approach to treatment.[27-29] The concept of a binocular approach to amblyopia treatment has been supported by recent evidence that binocular cortical mechanisms remain intact even in subjects with strabismic amblyopia.[30]

In 2010, Hess et al[27] reported a binocular paradigm for treatment of amblyopia consisting of laboratory-based dichoptic stimuli in which each eye was presented with a different stimulus. In these sessions, dichoptic motion coherence thresholds were measured, and contrast levels in the fellow eye were adjusted to optimize combination of visual information from both eyes and overcome suppression of the amblyopic eye. Nine adults (aged 24 to 49 years) were treated, with amblyopic-eye visual acuity ranging from 20/40 to 20/400. Treatment resulted in significantly improved amblyopic-eye visual acuity (P<0.008) and stereoacuity (P=0.012), despite 4 of 9 (44%) subjects previously being treated with patching. Knox et al[28] studied a similar paradigm with a binocular computer game using an in-office, head-mounted display over five 1-hour treatment sessions. Contrast was adjusted to equalize input from each eye. Fourteen children (aged 5 to 14 years) with previously treated amblyopia (patching) were included in the study, with amblyopic-eye visual acuity ranging from 20/25 to 20/200. Following treatment mean amblyopic-eye visual acuity had improved significantly (P=0.0001) despite previous treatment with patching. Six of the 14 children improved 0.1 logMAR or more and stereoacuity also improved significantly (P=0.02). In another recent study published in 2013, Li et al[31] used a video game, presented via head-mounted video goggles, one hour per day for two weeks of in-office sessions. Eighteen adults were treated in a crossover design comparing monocular game play with dichoptic game play, using adjustment of contrast to allow for binocular combination. Following treatment, dichoptic game play was found to significantly improve stereoacuity, visual acuity, and contrast balance between fellow and amblyopic eye compared with monocular game play. In these prior studies by Hess and Knox, of note is the finding that visual acuity improved despite prior treatment of amblyopia (44% of cases in Hess study and 100% in Knox study). Regarding amblyopia mechanism (strabismic, anisometropic, or combined), there was no evidence for one type of amblyopia to respond better with binocular amblyopia treatment.

These previous studies of binocular treatment have relied on in-office sessions to perform the respective binocular treatment paradigms, but Hess' group has recently adapted the binocular approach to a Hess Falling Blocks game platform on an iPod®[32, 33] and now on an iPad®. Using an iPod or iPad provides greater flexibility to the implementation of binocular treatment.

Previous studies of binocular treatment in children using an iPad format

Li et al (2014 in press) studied treating amblyopia with dichoptic iPad games, using red-green anaglyphic glasses, for 4 hours/week for 4 weeks, and reported a mean improvement from 0.47±0.03 logMAR at baseline to 0.39±0.03 logMAR (p<0.001) after 4 weeks of binocular treatment in 50 children age 4 to 12 years.[34] They found no significant mean improvement in visual acuity of 11 children assigned to sham treatment only 0.04±0.02 logMAR (p=0.1). Some children in each group also were treated with monocular patching, and at a different time of day,

at the discretion of the treating physician. Nevertheless, children treated with binocular games alone improved a mean of 0.08±0.02 logMAR. Although 4 games were available to each child, most children played the Hess Falling Blocks game or the balloon game (E. Birch, personal communication).

In a subsequent study in younger children (3 to <7 years), Birch et al reported no change in visual acuity with sham iPad games for 4 hours/week for 4 weeks (n=5), but an improvement from 0.43±0.03 logMAR to 0.34±0.03 logMAR in 45 children treated with dichoptic iPad games for 4 hours/week for 4 weeks ($p<0.001$).[35] Children who played the games 8 or more hours total playing time over the 4-week treatment period had significantly greater improvement than those who played 0-4 hours (0.14±0.02 logMAR vs 0.01±0.01 logMAR ($p=0.0001$)). Although these children were allowed to patch during the study (at the discretion of the treating physician), those who played ≥ 8 hours without patching showed an improvement of 0.14±0.05 logMAR at 4 weeks, which was no different than those who played ≥8 hours with patching (0.12±0.02 logMAR, $p=0.027$). Although 4 different games were available to each child, most children played the Hess Falling Blocks game or the balloon game (E. Birch, personal communication).

These studies provide "proof of concept" for the effectiveness of binocular treatment in amblyopia in children and adults, and demonstrate the feasibility of using the iPad format, wearing red-green anaglyphic glasses, for implementing binocular treatment in a pediatric population.

1.2 Rationale for an RCT and for the Proposed Study Design

Since current treatments for amblyopia have limited effectiveness in a notable proportion of children and preliminary studies in both children and adults have provided "proof of concept" that binocular treatment for amblyopia can be effective, a randomized clinical trial is needed to compare the effectiveness of binocular treatment to a current standard treatment, such as 2 hours of daily patching. We are not proposing an RCT comparing binocular treatment to sham binocular treatment or monocular treatment because that question has already been addressed in the pilot studies cited above.[31, 35]

Since patching 2 hours a day is effective in many younger children (age 5 to <13 years), we propose a non-inferiority study in this age group to test the hypothesis that binocular treatment is non-inferior to 2 hours of daily patching. If binocular treatment were found to be non-inferior to patching, then this finding would change practice because many children and parents would prefer to treat amblyopia without wearing a patch. We are not expecting age to affect the difference between binocular treatment and patching among 5- to <13-year olds because the decreasing effect of patching[36] with age appears to be paralleled by a decrease of effect of binocular treatment with age.[35] We therefore propose analyzing the age 5- to <13-year cohort together, estimating pooled variance from data on previous cohorts.

In teenagers (age 13 to <17 years) we have no evidence that patching is more effective than refractive correction alone (when including both previously untreated and previously treated subjects),[20] and therefore a non-inferiority study of binocular treatment versus patching cannot be justified. Nevertheless, the preliminary data of Hess et al[27, 32] suggests a robust effect of binocular treatment in adults, so we propose a superiority study design for 13- to <17-year olds, to test the hypothesis that binocular treatment is superior to 2 hours of daily patching. Including 2 hours of daily patching as one arm of a randomized trial in teenagers is considered ethical

because patching is prescribed by some clinicians for teenagers. If binocular treatment were found to be superior to patching in teenagers, then such a finding would clearly change practice because patching is relatively ineffective in this age group.

Regarding study duration, we recognize that the vast majority of available pilot data are from studies of only 4 weeks of treatment duration. Assessing the planned RCT primary outcome at 4 weeks was considered unreasonable because patching may take several months to show the majority of its effect.[11-15] On the other hand, assessing the primary outcome after a much longer duration of treatment, such as 6 months, was also considered unreasonable, because some children may be unwilling to play the games for many months. [34] Therefore we chose a compromise time point of 16 weeks for the primary outcome assessment, with planned secondary comparisons at 4, 8, and 12 weeks.

Regarding the dose of binocular treatment, pilot studies in adults by Hess et al[27, 32] primarily used one hour per day, whereas the pilot studies by Birch et al[35] in children used 4 hours a week. We therefore propose to prescribe "one hour a day, 7 days a week," with a minimum of 4 days for children unable to play 7 days a week.

Regarding choice of specific games to be used during the proposed study, game development has continued for the Hess Falling Blocks game, creating 3 levels of difficulty to allow play by children as young as 5 years, but with more difficult levels that will still engage teenagers. Because this game for binocular treatment is currently available with multiple levels of difficulty, and most available pilot data are with this binocular game, we plan to use only the Hess Falling Blocks game in the proposed RCT.

1.3 Study Objectives

- To compare the effectiveness of 1 hour/day of binocular game play 7 days per week (minimum of 4 days per week) with 2 hours/day patching 7 days per week, in children 5 to <13 years of age (younger cohort), as a non-inferiority study.
- To compare the effectiveness of 1 hour/day of binocular game play 7 days per week (minimum of 4 days per week) with 2 hours/day patching 7 days per week, in children 13 to <17 years of age (older cohort), as a superiority study.

1.4 Synopsis of Study Design

Major eligibility criteria: (*see section 2.2* for a complete listing)

- Age 5 to <17 years
- Amblyopia associated with anisometropia, strabismus (≤ 10Δ at near measured by PACT), or both
- No amblyopia treatment (atropine, patching, Bangerter, vision therapy) in the past 2 weeks
- Spectacles (if required) worn for at least 16 weeks, or demonstrated stability of visual acuity (<0.1 logMAR change by the same testing method measured on 2 exams at least 4 weeks apart)
- Visual acuity in the amblyopic eye 20/40 to 20/200 inclusive (33 to 72 letters if E-ETDRS)
- Visual acuity in the fellow eye 20/25 or better (≥78 letters if E-ETDRS)
- Interocular difference ≥3 logMAR lines (≥15 letters if E-ETDRS)
- No myopia greater than -6.00D spherical equivalent in either eye

- Ability to align the nonius cross on binocular game system. Heterotropia or heterophoria (total ocular deviation) ≤10Δ by PACT at near is allowed, as long as the subject is able to align the nonius cross.
- Demonstrate in-office ability to play the Hess Falling Blocks game (on easy setting) under binocular conditions (with red-green glasses) by scoring at least one line

Treatment Groups

Subjects will be randomly assigned (1:1) to either:

- Binocular treatment group: binocular computer game play prescribed 1 hour per day 7 days a week, with a minimum of 4 days for children unable to play 7 days a week (treatment time can be split into shorter sessions totaling 1 hour)
- Patching group: patching 2 hours per day for 7 days per week.

Sample Size – see details in Chapter 5

- 346 children aged 5 to < 13 years (younger cohort)
- 166 children aged 13 to < 17 years (older cohort)

Visit Schedule (timed from randomization)

- Enrollment exam
- 1 week phone call (7 to 13 days) to inquire about issues with the binocular game (if applicable) and to encourage compliance with treatment for both groups (to be completed by site personnel)
- 4 weeks ± 1 week
- 8 weeks ± 1 week
- 12 weeks ± 1 week
- 16 weeks ± 1 week (primary outcome)

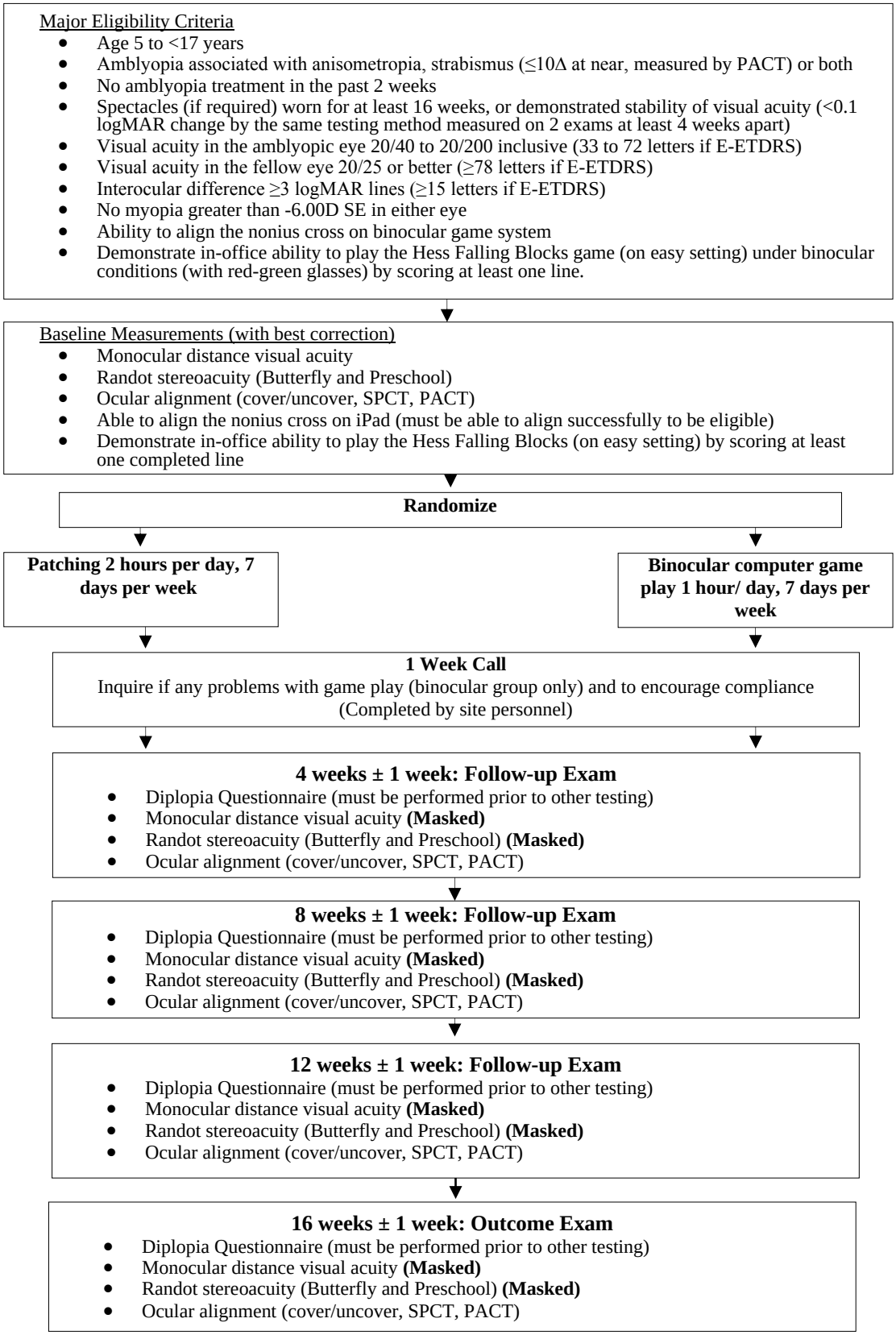
All subjects will be seen at 4, 8, 12, and 16 weeks after randomization. Subjects achieving amblyopic-eye visual acuity equal to or better than the fellow-eye visual acuity (0 or more lines better with ATS-HOTV, or 0 or more letters better with E-ETDRS) and at least 20/25 (or ≥78 letters if E-ETDRS) visual acuity in both eyes will be considered to have resolved and will discontinue treatment, although these subjects will still return for all remaining follow-up exams. If at a subsequent visit there is regression of amblyopia (≥ 2 logMAR lines or ≥ 10 letters from the best previous visual acuity), treatment will be restarted.

At each follow-up visit, we will assess distance visual acuity in each eye using ATS-HOTV for children <7 years at enrollment and the E-ETDRS for children ≥7 years at enrollment. We will also assess stereoacuity using the Randot Butterfly Stereoacuity test and Randot Preschool Stereoacuity test, history of diplopia, and ocular alignment by cover uncover test, simultaneous prism cover test (SPCT) (if deviation present), and prism and alternate cover test (PACT).

Analysis

The primary analysis in the younger cohort (ages 5 to < 13 year) will be a non-inferiority analysis of mean visual acuity change from enrollment at 16 weeks in the binocular computer treatment group compared with the patching group. The primary analysis in the older cohort (ages 13 to < 17 years) will be a superiority analysis of mean visual acuity change from enrollment at 16 weeks in the binocular treatment group compared with the patching group.

Study Summary Flow Chart



CHAPTER 2: SUBJECT ENROLLMENT

2.1 Eligibility Assessment and Informed Consent/Assent

The study plans to enroll a minimum of 346 subjects aged 5 to <13 years and up to 166 subjects aged 13 to <17 years. As there will be a planned interim analysis for futility in the older cohort, it is possible that less than 166 subjects will be enrolled (*see Chapter 5).* As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized until the end date, which means the expected recruitment might be exceeded.

A child is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard of care) that identifies amblyopia appearing to meet the eligibility criteria. The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)). Parent(s) who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent / assent must be obtained from a parent and child prior to performing any study-specific procedures that are not part of the child's routine care.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility Criteria

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

1. Age 5 to <17 years
2. Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated)
   a. Criteria for strabismus: At least one of the following must be met:
      - Presence of a heterotropia on examination at distance or near fixation (with or without spectacles)
      - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia)
   b. 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
   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*
3. No amblyopia treatment in the past 2 weeks (patching, atropine, Bangerter, vision therapy)
4. Refractive correction (spectacles or contact lenses, if applicable) must meet the following criteria at enrollment and be based on a cycloplegic refraction that is not more than 7 months old.
   a. Requirements for Correction of Refractive Error:
      1) For subjects meeting criteria for strabismic (only) amblyopia (*see 2.2.1 #2 above*):
         - Hypermetropia, if corrected, must not be under-corrected by more than +1.50 D spherical equivalent, and the reduction in plus sphere must be symmetric in the two eyes.

2) For subjects meeting criteria for anisometropic or combined-mechanism amblyopia (*see 2.2.1 #2 above*):
   - Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
   - Hypermetropia must not be under-corrected by more than +1.50 D spherical equivalent, and reduction in plus 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 for both eyes must be within 6 degrees of the axis of the cycloplegic refraction when cylinder power is ≥1.00 D

b. Refractive corrections meeting the above criteria must be worn for either:
   - 16 weeks or more or
   - Until visual acuity in amblyopic eye is stable (defined as 2 consecutive visual acuity measurements by the same testing method at least 4 weeks apart with <1 line change (<5 letters if E-ETDRS))

c. Monocular or binocular contact lens wear is allowed provided the contact lenses meet the above refractive requirements at the corneal plane. The same form of correction must be worn throughout the entire study during study procedures (i.e., no changing between contacts and spectacles while patching or while game-playing or study testing). Safety glasses are not required for subjects wearing contact lenses, but investigators are encouraged to suggest safety glasses be worn over contact lenses.

5. Visual acuity, measured in each eye without cycloplegia in current refractive correction (if applicable) within 7 days prior to randomization using the ATS-HOTV visual acuity protocol for children < 7 years and the E-ETDRS visual acuity protocol for children ≥ 7 years on a study-approved device displaying single surrounded optotypes, as follows:
   a. Visual acuity in the amblyopic eye 20/40 to 20/200 inclusive (33 to 72 letters if E-ETDRS)
   b. Visual acuity in the fellow eye 20/25 or better (≥ 78 letters if E-ETDRS)
   c. Interocular difference ≥ 3 logMAR lines (≥ 15 letters if E-ETDRS) (i.e., amblyopic-eye acuity at least 3 logMAR lines worse than fellow-eye acuity)
6. Heterotropia or heterophoria with a total near deviation of ≤ 10Δ (measured by PACT).
7. Ability to align the nonius cross on the binocular game system (angles of ocular deviation >10Δ would require the nonius cross to be adjusted to such an extent that playing of the game would be compromised).
8. Subject is able to play the Hess Falling Blocks game on the study iPad (on easy setting) under binocular conditions (with red-green glasses), as demonstrated by scoring at least 1 line in the office.
9. Investigator is willing to prescribe computer game play or patching per protocol.
10. Parent understands the protocol and is willing to accept randomization.
11. Parent has phone (or access to phone) and is willing to be contacted by Jaeb Center staff.
12. Relocation outside of area of an active PEDIG site for this study within the next 16 weeks is not anticipated.

2.2.2 Exclusion Criteria

A subject is excluded for any of the following reasons:

1. Prism in the refractive correction at time of enrollment (eligible only if prism is discontinued 2 weeks prior to enrollment).

2. Myopia greater than -6.00D spherical equivalent in either eye.
3. Previous intraocular or refractive surgery.
4. Any treatment for amblyopia (patching, atropine, Bangerter filter, or vision therapy) during the past 2 weeks. Previous amblyopia therapy is allowed regardless of type, but must be discontinued at least 2 weeks immediately prior to enrollment.
5. Ocular co-morbidity that may reduce visual acuity determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the subject if the above visual acuity criteria are met*).
6. No Down syndrome or cerebral palsy
7. No severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delay or reading and/or learning disabilities are not excluded.
8. Heterotropia or heterophoria with a total ocular deviation >10Δ (phoria plus tropia >10Δ) at near (measured by PACT).

2.3 Historical Information

Historical information to be elicited will include the following: date of birth, sex, race, ethnicity, and history of prior eye-related treatment (including length of spectacle wear).

2.4 Procedures at the Enrollment Visit

All examination procedures must be tested within 7 days prior to the date of enrollment, except the cycloplegic refraction and ocular examination, which may be performed within 7 months prior to enrollment. All examination procedures at enrollment are performed in the subject's current correction, if required (testing in trial frames is not permitted), and without cycloplegia:

1. Distance Visual Acuity Testing: Monocular distance visual acuity testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-HOTV visual acuity protocol for children <7 years and the E-ETDRS visual acuity protocol for children ≥ 7 years on a study-certified acuity tester displaying single surrounded optotypes as described in the *ATS Testing Procedures Manual*.
   - Testing must be completed without cycloplegia and with spectacles or contact lenses, if worn (trial frames not allowed at enrollment)
   - The same visual acuity protocol will be used throughout the study regardless of age at follow-up.

2. Stereoacuity Testing:
   - Stereoacuity will be tested at near in current refractive correction using the Randot Butterfly and Randot Preschool stereoacuity tests.

3. Ocular Alignment Testing:
   - Ocular alignment will be assessed in current refractive correction by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter) as outlined in the *ATS Procedures Manual*.
     - See *section 2.2.1* for eligibility criteria related to ocular alignment.

4. Additional Clinical Testing:
   - Ocular examination as per investigator's clinical routine (if not performed within 7 months)

5. Nonius Cross Alignment

- Subjects will be tested to see if they are able to align the nonius cross presented on the iPad. Subjects unable to fuse the cross are not eligible for the study.

6. Demonstration of Game Understanding

Subjects must demonstrate that they understand the game by scoring at least one completed line while playing the game set to the easy level in the office. Subjects unable to score a line are not eligible for the study.

2.5 Randomization of Eligible Subjects

The Jaeb Center will construct a Master Randomization List using a permutated block design stratified by site and age subgroup (5 to <7 years versus 7 to <13 years) in the younger cohort (5 to <13 years), and stratified by site and baseline amblyopic-eye visual acuity (20/40 to 20/80 (53 to 72 letters) and 20/100 to 20/200 (33 to 52 letters)) in the older cohort (13 to <17 years), which will specify the order of treatment group assignments. Although we would ideally stratify by each of three factors (site, age subgroup, and baseline amblyopic acuity) in both the younger and older cohorts, this was unlikely to achieve the desired balance given the proposed sample size, and so the 2 most important factors were chosen, within each age cohort, for stratification. Randomization will not be stratified by presence of a tropia since diagnosis of a microtropia is problematic.

All eligible subjects enrolled in the study will be randomly assigned in a 1:1 allocation to one of the following groups for each of the age cohorts:

- Binocular treatment group: binocular computer game play 1 hour per day, 7 days per week (minimum of 4 days per week)
- Patching group: Patching 2 hours per day, 7 days per week.

Once a child is assigned to treatment, he/she will be included in the analysis regardless of whether or not the assigned treatment is received. Thus, the investigator must not randomly assign a subject to treatment unless convinced that the parent will accept either of the treatments.

CHAPTER 3: TREATMENT AND FOLLOW-UP

3.1 Binocular Computer Game Treatment

All subjects in the study will play the Hess Falling Blocks game presented on an iPad while wearing red/green (anaglyph) glasses (over current spectacles, if applicable) with the green filter placed over the amblyopic eye. The subject should be instructed to hold the iPad at his/her usual reading distance. Some boxes are only visible to the fellow eye viewing through the red lens, while other boxes are only visible to the amblyopic eye viewing through the green lens. Image contrast varies depending on depth of amblyopia to ensure stimulation of the amblyopic eye and binocular game play.

Contrast of the falling shapes in the amblyopic eye will be at 100% throughout the study. Contrast of shapes seen by the fellow eye will begin at 20% at the start of the study and will increase or decrease automatically in 10% increments from the last contrast level (e.g., 20% to 22%) in a 24-hour period based on the subject's performance and duration of game play. As the ability of the subject to use the amblyopic eye improves, game performance is expected to increase, and therefore the contrast setting in the fellow-eye will increase. The lower limit of fellow-eye contrast is set at 10%, which corresponds to the lower limit of the visible threshold for viewing objects on the screen. If the fellow-eye contrast remains at 10% for a period of 7 days, the game will show an alert for parents to contact their eye care provider.

3.1.1 Binocular Treatment Group

Subjects assigned to the binocular treatment group will be prescribed the Hess Falling Blocks game to play for 1 hour per day, 7 days a week (with a minimum of 4 days a week for children unable to play 7 days a week) for 16 weeks. Parents of subjects will be instructed that the 1 hour of daily treatment should be completed in a single 60-minute session, but if this is not possible for whatever reason, the treatment may be divided into shorter sessions totaling 1 hour. The difficulty setting (easy, medium, or hard) is at the discretion of the child.

3.1.2 Patching Group

Subjects assigned to the patching group will wear an adhesive patch over the fellow eye for 2 hours per day, 7 days per week for 16 weeks. Parents of subjects will be instructed that the 2 hours of daily patching should be completed in a single 2-hour session, but if this is not possible for whatever reason, the treatment may be divided into shorter sessions totaling 2 hours.

3.2 Compliance

Parents will be asked to complete a compliance calendar by manually recording the number of minutes that the child played the game each day or how long the patch was worn. The investigator will review the calendars at each follow-up visit. The amount of time the game is played will also be recorded automatically during game play by the iPad. These data will be downloaded at the site during each follow-up visit when the iPad is brought to the study visit.

3.3 Phone Call

Site personnel will call all subjects at 1 week (7 to 13 days) to encourage compliance with treatment and to confirm that there are no technical problems playing the binocular game for those assigned to binocular treatment.

3.4 Follow-up Visit Schedule

The follow-up schedule is timed from randomization as follows:

- 4 weeks ± 1 week
- 8 weeks ± 1 week
- 12 weeks ± 1 week
- 16 weeks ± 1 week

Subjects achieving amblyopic-eye visual acuity equal to or better than the fellow-eye visual acuity (0 lines or more lines better, 0 letters or more better if E-ETDRS) and at least 20/25 (or ≥78 letters if E-ETDRS) visual acuity in both eyes will be considered to have resolved and will discontinue treatment, although these subjects will still return for all remaining follow-up exams. If at a subsequent visit there is regression of amblyopia (2 logMAR lines or 10 letters from best previous visual acuity), treatment will be restarted.

Additional non-study visits can be performed at the discretion of the investigator.

3.5 Follow-up Visit Testing Procedures

Subjects will be seen at follow-up visits as outlined in *section 3.4*. A Masked Examiner must complete distance visual acuity and stereoacuity testing at these visits (*section 3.5.*1). All procedures will be performed with the subject's current refractive correction. If a subject currently wears spectacles but is not wearing them at the follow-up examination for whatever reason, testing must be performed in trial frames.

Prior to the Masked Examiner entering the room, subjects and parents should be instructed not to discuss their treatment with the Masked Examiner.

The following procedures should be performed at each visit:

1. Diplopia Questionnaire
   - The child and parent(s) will be specifically questioned regarding the presence and frequency of any diplopia since the last study visit using a standardized diplopia assessment (*see ATS Miscellaneous Testing Procedures Manual*). The diplopia assessment must be performed prior to any other testing during the exam.

2. Distance Visual Acuity Testing (masked):
   - Monocular distance visual acuity testing will be performed in habitual refractive correction in each eye using the same visual acuity testing method that was used at enrollment, as described in the *ATS Testing Procedures Manual*.
   - Testing must be completed without cycloplegia.

3. Stereoacuity Testing (masked):
   - Stereoacuity will be tested in habitual current refractive correction using the Randot Butterfly test and Randot Preschool Stereoacuity test at near (1/3 meter).

4. Ocular Alignment Testing:
   - Ocular alignment will be assessed in habitual refractive correction by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test

(PACT) in primary gaze at distance (3 meters) and at near (1/3 meter) as outlined in the *ATS Procedures Manual*.

3.5.1 Masked Examiner

The Masked Examiner must be certified to test visual acuity and stereoacuity. Because the Masked Examiner must be masked to the subject's treatment group, he/she must be someone other than the managing clinician (in many cases the managing clinician will be the investigator but this is not required).

3.6 Non-Study Visits and Treatment

Investigators may schedule additional visits at their own discretion. Subjects will continue to follow the study-specified follow-up schedule regardless of any non-study visits. No data will be collected at non-study visits for the purpose of the study.

Investigators must not start any additional treatment (other than that outlined in *section 3.1*) prior to the 16-week outcome visit.

CHAPTER 4: MISCELLANEOUS CONSIDERATION IN FOLLOW-UP

4.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent's contact information. The Jaeb Center may contact the parents of the subjects. 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 subject and/or family and to help coordinate scheduling of the outcome examinations.

The site investigator or coordinator will contact the parents of each subject after the first week of the study to encourage compliance with treatment and to confirm that there are no technical problems playing the binocular game for those assigned to binocular treatment.

4.2 Game Alerts

In the event that the subject is unable to successfully play the game for whatever reason (e.g., failure of amblyopia to improve, worsening of amblyopic eye, inattention of subject), contrast of the fellow eye will automatically decrease in 10% increments, to as low as 10%, which corresponds to the lower limit of the visible threshold for viewing objects on the screen. If the game settings remain at 10% for a period of 7 days, the game will show an alert for parents to contact their eye care provider. Investigators should assess the cause for the inability to play the game. As appropriate, investigators may choose to examine the subject at their discretion and contact the Jaeb center for technical assistance if deemed necessary. Investigators will offer encouragement to the child and parents to continue treatment as best they are able.

4.3 Subject Withdrawals

Parents may withdraw their child from the study at any time. This is expected to be a very infrequent occurrence in view of the study design's similarity to routine clinical practice and short duration. If the parents indicate that they want to withdraw their child from the study, the investigator personally should attempt to speak with them to determine the reason. If their interest is in transferring the child's care to another eye care provider, every effort should be made to comply with this and at the same time try to keep the child in the study under the new provider's care.

4.4 Management of Refractive Error

Because of the short duration of the study and the requirement to have a cycloplegic refraction within 7 months prior to enrollment, no cycloplegic refraction is mandated during the study. Nevertheless, whenever the investigator suspects that refractive error may not be corrected according to study guidelines, a cycloplegic refraction should be performed. Change in spectacle correction is at investigator discretion, but must be prescribed according to the guidelines described in *section 2.2.1*.

4.5 Management of Strabismus

Because of the short duration of the study and the age group being studied, strabismus surgery is not allowed prior to the end of the study (at 16 weeks). If surgery is performed that occurrence will be recorded in the comment section of the Follow-up Examination Form.

4.6 Risks

4.6.1 Development of Manifest Ocular Deviation or Diplopia

The study treatment could possibly precipitate the development of a manifest ocular deviation. The development of a new manifest ocular deviation is an accepted risk of amblyopia therapy as part of standard care. Such an event occurred with both patching and atropine therapy in previous studies of patching versus atropine[11-15] (about 12% of cases in both groups). Nevertheless, 13% of subjects had resolution of their pre-existing manifest ocular deviation >8Δ with amblyopia treatment. In previous studies of treating amblyopia in adult subjects using binocular computer game play,[27] no subject developed a new manifest ocular deviation, therefore the risk of developing a new heterotropia in this study is not expected to be any greater than it would be with standard care treatment of amblyopia.

Diplopia has been considered to be a possible adverse effect of treating amblyopia in older children. However, in our previous study of older children (age 7 to <17 years),[20] no subjects developed constant diplopia during the randomized trial phase. In the 7- to <13-year-old subjects[20] not reporting diplopia at baseline, intermittent diplopia occurring more than once per day was reported by 4 subjects in the patching plus atropine group and by 1 subject in the optical correction group. For 3 of the 4 subjects in the patching plus atropine group, diplopia was not reported at the last study visit; 1 subject at the last visit reported diplopia once a day, while the parent reported the diplopia occurred once a week. While still on treatment after the end of the randomized trial phase, an 8-year-old subject in the patching plus atropine group, who had a history of a prior sixth nerve palsy and esotropia at near at baseline, developed intermittent daily diplopia; at the last visit the subject indicated diplopia was occurring several times a day but the parent indicated once a week. In the 13- to <17-year-old subjects in that study,[20] there were no reports of diplopia occurring more than once per day. In previous studies using binocular computer game play for treatment of amblyopia,[27, 34, 35] no subjects reported development of diplopia during treatment. Data on frequency of diplopia will be collected from the child and parent(s) at each study visit.

If treatment precipitates the development of a manifest ocular deviation (e.g., esotropia) and/or diplopia, the parent will be advised to have the subject see the investigator as soon as possible. If a new manifest deviation is confirmed on examination, the decision as to whether to continue or discontinue therapy will be left to the investigator's and parent's decision. If the investigator determines that binocular diplopia is present, continuation of treatment is also at the discretion of the investigator and parent(s). If amblyopia treatment is to be discontinued during the study, a Protocol Chair should be called to discuss the case. Subjects discontinuing treatment during the study will continue to be seen for the remaining regularly scheduled study visits.

4.6.2 Risks of Examination Procedures

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

4.6.3 Risks of Patching

If skin irritation occurs, the parent will be advised to put an emollient on the skin and discontinue use of the patch for a day.

Patching could potentially decrease the visual acuity in the fellow eye, although this is almost always reversible. However, this occurrence is extremely unlikely since the fellow eye will have the

majority of the day without occlusion and we have not observed long lasting decrease in visual acuity in any previous study of 2 hours of daily patching. The diagnosis and management of reverse amblyopia is left to the investigator's judgment.

4.6.4 Delay in Use of Traditional Amblyopia Treatment

The subjects in the binocular computer game treatment group will not be able to perform any patching, atropine, Bangerter filter, or vision therapy treatment during the study. Subjects will continue in the study for a maximum of 16 weeks. Subjects in the patching group will not be able to start any additional treatment or change the duration of patching during the study.

4.7 Reporting of Adverse Events

No surgical procedures are part of the protocol. There are no expected long-term adverse events associated with playing the computer game on the iPad. Investigators will abide by local IRB reporting requirements.

4.7.1 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.

4.8 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 subjects.

4.9 Travel Reimbursement

Parents of each subject will be compensated $50 per visit (by check, merchandise card, or money-card) for completion of each protocol-specified visit, for a maximum of $250. If there are extenuating circumstances, and the subject is unable to complete study visits without additional funds for travel costs, additional funds may be provided.

4.10 Study Costs

The subject or his/her insurance provider will be responsible for the costs that are considered standard care.

Because the treatment used in the study is not standard, the enrollment, 4-, 8-, 12-, and 16-week follow-up visits are not considered standard of care and will be paid for by the study. The cost of the patches and the binocular game treatment related equipment will also be paid for by the study; however the iPad will need to be returned upon study completion. Cost of changing or replacing prescription glasses (or contact lenses) either before or during the study will not be paid for by the study as spectacle correction is standard care.

4.11 Offer of Binocular Treatment to Children Assigned to Patching (at Conclusion of Study)

To reduce the potential disincentive to participation because there is only a 50% chance of receiving the novel binocular treatment at enrollment, subjects assigned to the patching group with residual amblyopia at the conclusion of their participation in the study will be offered 16 weeks of binocular

game therapy using a study iPad (at no cost). Subjects (originally assigned to patching) who elect to pursue 16 weeks of binocular treatment after study completion, will return the iPad devices to the site at the conclusion of that additional treatment. No data will be collected from these subjects.

CHAPTER 5: 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.

5.1 Definition of Subject Cohorts

The study will enroll two cohorts of subjects with identical eligibility criteria, apart from age at time of randomization:

- Younger Cohort: children aged 5 to < 13 years
- Older Cohort: children aged 13 to <17 years

These cohorts will be analyzed separately as the objectives differ.

5.2 Sample Size Estimation

Sample size estimates for each age cohort were based on data from previous ATS patching studies, limited to subjects meeting the visual acuity eligibility criteria for the current protocol.

5.2.1 Younger Cohort (Children 5 to <13 years of age)

The standard deviation for change in amblyopic eye visual acuity at 16-weeks was estimated to be 0.15 logMAR from previous ATS studies.[37-39] The 95% confidence interval for the standard deviation was 0.13 to 0.16 logMAR. These were used to compute sample sizes in the table below:

Total Sample Size Estimates
Based on 90% Power*

Standard Deviation (logMAR)	Noninferiority Limits (difference in logMAR)			
	0.050	**0.055**	**0.060**	**0.075**
0.13	234	194	164	106
0.14	270	224	188	122
0.15	310	258	216	140
0.16	354	292	246	158

* Based upon alpha = 0.05 for 1-sided t-test. Cells reflect total sample size needed

Based on a standard deviation of 0.15 logMAR, a sample size of 310 subjects was chosen (155 per group) in order to have 90% power for a non-inferiority hypothesis test, assuming that the true difference between the two treatments is zero with a non-inferiority limit of 0.05 logMAR. A total sample size of 346 (173 per group) was computed after adjustment for 10% loss to follow-up.

Interim Monitoring

There are no plans to conduct interim monitoring for efficacy and/or futility given there are no safety concerns or health risks with either treatment, and subjects will have access to the alternate treatment after completing the study. In addition, based on pilot data of binocular therapy in this age group[35], it is unlikely that the treatment effect of patching is sufficiently superior to binocular therapy to allow criteria for futility stopping to be met at an interim analysis. Finally, early stopping for efficacy would reduce power for the planned test of superiority of binocular therapy in the event that binocular treatment is declared non-inferior to patching.

5.2.2 Older Cohort (Children 13 to <17 years of age)

The standard deviation for change in amblyopic eye visual acuity at 16-weeks was estimated to be 9.0 letters from previous ATS studies.[20] The 95% confidence interval for the standard deviation was 5.8 to 10.1 letters. These were used to compute sample sizes in the table below:

Total Sample Size Estimates
Based on 90% Power*

Standard Deviation (letters)	Mean Change from Baseline in Visual Acuity at 16-weeks (letters)		
	3.75	**5.0**	**6.25**
6.0	110	64	42
7.0	150	86	56
8.0	194	110	72
9.0	246	140	90
10.0	302	172	110

* Based upon alpha = 0.05 for 2-sided t-test. Cells reflect total sample size needed

Based on a standard deviation of 9 letters, a sample size of 140 subjects was chosen (70 per group) in order to have 90% power to detect a treatment group difference if the true difference in mean visual acuity change between treatment groups is 5.0 letters (1 line) at 16 weeks. Adjusting for 10% loss to follow-up, a total sample size of 156 (78 per group) is needed.

Interim Monitoring

Interim monitoring for futility will be conducted for the older cohort. Although there is some evidence to suggest that binocular treatment may be better than patching in older children, the potential for poor compliance with binocular treatment in this age group is a concern, and could increase the chance that binocular treatment cannot be demonstrated to be better than patching.

Guidelines and provisions for futility stopping will be established prior to any tabulation or analysis of outcome data. Details of the interim monitoring plan will be developed in consultation with the DSMC and will be included in the statistical analysis plan. A sample size adjustment of 5% will be applied to account for loss of power due to interim futility monitoring, resulting in a final sample size of 166 subjects (83 per group).

5.3 Primary Analysis

Two treatment approaches will be evaluated within each of the age cohorts as follows:

1. Binocular treatment: Binocular computer game play 1 hour per day, 7 days per week (minimum of 4 days per week)
2. Patching treatment: Patching 2 hours per day, 7 days per week

An analysis of covariance (ANCOVA) will be performed to compute the 16-week mean change in visual acuity for each treatment group, adjusted for baseline acuity and baseline age, and a 95% confidence interval will be constructed on the treatment group difference. Linearity assumptions will be evaluated for baseline visual acuity and baseline age and these factors will be treated as continuous covariates if the model assumptions are met.

For the younger age cohort (5 to <13 years of age), the upper limit of a 1-sided 95% confidence interval on the treatment effect (Patching – Binocular treatment) will be compared with the non-

inferiority limit of 0.05 logMAR. Non-inferiority of binocular treatment will be declared if the upper 1-sided confidence interval limit is less than the non-inferiority margin of 0.05 logMAR. In the event that non-inferiority of binocular treatment is declared, a test for superiority of binocular treatment will be performed using the same 95% confidence interval and pre-specified margin.

For the older age cohort (13 to <17 years of age), superiority of binocular treatment will be declared if the treatment effect (Binocular treatment – Patching) is positive and the 95% confidence interval on the treatment group difference in mean visual acuity change excludes zero.

The primary analysis will follow the intent-to-treat principle. Data will be included only from subjects who complete the 16-week exam within the predefined analysis window. There will be no imputation of data for subjects who are lost to follow-up or withdraw from the study prior to the 16-week exam. In a secondary approach to the primary analysis, multiple imputation for missing data will be performed and results of the analysis with imputation of missing data assessed for consistency with the primary analysis. A separate analysis also will be conducted including only subjects whose outcome exams were performed within the protocol time window for the visit.

5.4 Secondary Analyses

Secondary analyses will be conducted separately for both the primary and the secondary study cohorts. All treatment group comparisons will consist of a test of the usual null hypothesis of no difference between groups; the non-inferiority hypothesis will not be tested in secondary analyses for the younger cohort.

5.4.1 Visual Acuity Defined as a Binary Outcome

Secondary analyses will estimate the proportion of subjects who achieve the following visual acuity outcomes by treatment group:

- Amblyopic-eye visual acuity improvement of 2 or more logMAR lines (10 or more letters if E-ETDRS) 16 weeks after randomization
- Resolution of amblyopia at 16 weeks after randomization, defined as amblyopic-eye visual acuity of 20/25 or better (≥78 letters) and within 1 logMAR line (≤5 letters) of the fellow-eye acuity.

The proportion of subjects who achieve each outcome will be tabulated by treatment group and an exact 95% confidence interval will be computed on the group proportion. A p-value for the treatment group comparison will be computed using binomial regression with adjustment for baseline visual acuity. If the binomial regression model does not converge, Poisson regression with robust variance estimation or an exact method (without baseline adjustment) will be used to derive a p-value for the treatment group comparison.

5.4.2 Time Course of Visual Acuity Improvement

A secondary analysis will compare treatment groups with respect to the time course of change in visual acuity.

A linear mixed ANCOVA model will be used to compare the rate of visual acuity improvement between the two groups. A regression line will be fit for visual acuity over time for each treatment group and the slope of these lines will be compared by including an interaction term with treatment group and time in the ANCOVA model, adjusted for baseline acuity and main effects of the interaction term. If the interaction term is not statistically significant ($p > 0.05$), then no further

comparisons will be computed. However, if the interaction term is statistically significant, then a comparison of mean visual acuity by treatment group at each time point (0 – baseline, 1 – 4 weeks, 2 – 8 weeks, 3 – 12 weeks, 4 – 16 weeks) will be performed using linear contrasts.

Prior to performing the ANCOVA, the time course of change in visual acuity in each group will be plotted to determine whether data transformation is needed to linearize the relationship between time and visual acuity improvement. In the event that a suitable transformation to linearize the relationship cannot be found, a discrete time model will be used. Exploratory analyses will be conducted to determine the correction structure over time of the data, and to choose a suitable correlation structure for use in the mixed ANCOVA model.

5.4.3 Subgroup Analysis

The treatment effect in subjects based on baseline factors will be assessed in exploratory analyses. Analyses of subgroups will be considered exploratory and used to suggest hypotheses for further investigation in future studies.

The subgroups of interest include the following: amblyopic-eye visual acuity, age (in younger cohort only), the presence of a tropia, and prior amblyopia treatment.

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 differential treatment effect by these variables is not expected.

The general approach for these exploratory analyses will be to conduct an analysis of covariance similar to the primary analysis including an interaction for treatment and the subgroup covariate of interest. If the overall F-test for interaction is not statistically significant ($p > 0.05$), then no subgroup comparisons will be computed, but this will not be interpreted as conclusive evidence of no subgroup effect given that power for the tests of interaction is low.

The subgroup definitions for the planned subgroup analyses are as follows:

- Amblyopic-eye visual acuity at baseline (20/40, 20/50, 20/63, 20/80 or worse)
- Presence of a heterotropia at baseline (yes/no)
- Age (years) at baseline (5 to <7, 7 to <13)
- Prior amblyopia treatment (yes/no)

5.4.4 Treatment Compliance (Binocular computer treatment group)

Compliance will be evaluated for each treatment group based on both the parent-completed compliance calendars and automated iPad program logs. For the latter, the distribution of the total time spent playing the iPad program will be calculated based on the program logs. Both total play time since baseline and total play time since the previous visit will be computed. Compliance will be assessed at 4, 8, 12, and 16 weeks and the relationship between visual acuity improvement and total play time will be evaluated at 16 weeks.

5.4.5 Stereoacuity

Change in stereoacuity from baseline to 16 weeks will be tabulated for each group and compared between treatment groups using the exact Wilcoxon rank-sum test.

5.4.6 Fellow-eye Contrast (Binocular computer treatment group)

Contrast of the fellow eye will be tabulated for the binocular computer treatment group based on automated iPad program logs at 4, 8, 12, and 16 weeks.

5.4.7 Safety

5.4.7.1 Visual Acuity in Fellow Eye

The mean change in fellow-eye visual acuity from baseline to 16 weeks will be calculated and compared between treatment groups using ANCOVA with adjustment for baseline visual acuity. The proportion of subjects with loss of 2 or more logMAR lines (10 or more letters) of visual acuity in the fellow eye from baseline to the 16-week exam will be reported for each treatment group and compared using the Fisher exact test.

5.4.7.2 Ocular Alignment

The proportion of subjects with development of new strabismus (no heterotropia at baseline and the presence of near and/or distance heterotropia at 16 weeks) or an increase from baseline $\geq 10\Delta$ in a pre-existing strabismus will be reported by treatment group and compared using the Fisher exact test.

5.4.7.3 Diplopia

The proportion of subjects with each category of diplopia will be reported by treatment group and compared using the Fisher exact test.

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