AMBLYOPIA TREATMENT STUDY (A10)

A Randomized Trial of Full-time Bangerter Filters versus Part-time Daily Patching for the Treatment of Moderate Amblyopia in Children

PROTOCOL

Version 2.0

November 6, 2007

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1 Background

Amblyopia is the most common cause of monocular visual impairment in children, estimated to affect as many as 3.6% of the childhood population.[1] The natural history of amblyopia is relatively unknown although it has been reported that visual acuity may deteriorate further without treatment.[2,3]

Although occlusion or patching of the sound eye has been the mainstay for amblyopia therapy, alternative treatment such as pharmacological or optical penalization may be as effective.[4-6] In a randomized, controlled clinical trial of 419 children, 3 years to less than 7 years old with moderate amblyopia, patching was compared to atropine.[7] Although improvement with atropine was initially slower, both treatments produced similar improvement after 6 months.

Although both patching and atropine have been proven effective for treating amblyopia, neither treatment is without adverse side effects. Patching is associated with compliance difficulties, the need for continuous monitoring, and social stigma. Negative side effects observed in children treated with atropine include light sensitivity, facial flushing, and fever.[7] In a randomized clinical trial comparing patching to atropine as a treatment for amblyopia, a questionnaire to assess the impact of patching and atropine treatment on the child and family indicated that both treatments were well tolerated overall, however, patching had lower compliance and higher social stigma than atropine.[8]

Another treatment option for amblyopia is Bangerter occlusion foils or filters. Bangerter foils were introduced in 1960 to provide graded reduction of image quality to the sound eye.[9] The filters are available in graded densities designed to reduce visual acuity to a range of 20/25 to 20/300. Table 1 shows filter densities and corresponding levels to which normal visual acuity is degraded by the filter, according to the manufacturer. The filters are worn on the back surface of the spectacle lens in front of the sound eye. One advantage of Bangerter filters compared with patching is that the lower density filters are not readily apparent and therefore would be expected to increase patient compliance due to reduced social stigma. Another advantage of Bangerter filters is that there is no opportunity for skin irritation from bandage adhesive, a commonly-reported side effect of patching[7]. In addition, there is a theoretical advantage that Bangerter foils are less disruptive to binocular function during treatment compared with other modalities such as patching. Disadvantages of Bangerter foils are that glasses must always be worn during treatment, it is easy to peek around the glasses, the foils may not degrade visual acuity to the labeled level, and the foils become soiled and fade with time, thus losing their treatment effect if not replaced frequently. Also, the relative rate at which Bangerter filters improve acuity has not been directly compared with patching or atropine. Bangerter filters are often prescribed for longer periods than either patching or atropine.

Table 1. Bangerter Filter Densities

Filter Density	Visual Acuities*
1.0	˜20/20
0.8	˜20/25
0.6	˜20/30
0.4	˜20/50
0.3	˜20/70
0.2	˜20/100
0.1	˜20/200
<0.1	˜20/300
Light Perception	Light Perception

*Visual acuity level to which normal visual acuity is labeled to be degraded by the filter.

Bangerter foils have been used mainly as secondary amblyopia therapy following patching or atropine to either further improve or maintain the visual gain. Iacobucci and associates[10] treated 18

children with Bangerter foils who had been previously treated with patching. Children were changed to Bangerter foils because of either non-compliance with patching (10 patients) or lack of further improvement with patching (8 patients). At the time patching treatment had been prescribed, children ranged in age from 2-8 years old and had amblyopic eye acuities ranging from 20/30 to 20/200, with most acuities (10 of 18) between 20/40 and 20/60. Patching treatment was continued for a mean of 8.5 months. Bangerter foil treatment was initiated the same day patching was discontinued, at which time children had amblyopic eye visual acuity ranging from 20/25 to 20/60, with most having acuity of 20/30 (8 of 18). After treatment with Bangerter foils for a mean duration of 8 months, two thirds of patients (12 of 18) obtained amblyopic eye acuity of 20/20 or equal to that of the sound eye. Of the remaining 6 patients, 5 obtained amblyopic eye acuity of 20/25 or 20/30 or within a half-line of the sound eye.

Bangerter foils have been used as primary therapy for moderate amblyopia, although there are few reports addressing their efficacy or effectiveness. As a primary treatment of amblyopia, Iacobucci and associates[10] used Bangerter foils to treat 15 children, 3 to 8 years old, with amblyopia of 20/30 to 20/60 for a mean duration of 9 months. Two-thirds of patients (10 of 15) obtained amblyopic eye acuity of 20/20 or better or equal to that of the sound eye. Of the remaining 5 patients, 4 attained amblyopic eye acuity of 20/25 or 20/30 or within a half-line of the sound eye.

There is little consensus as to which density Bangerter foil should be used initially when treating amblyopia. The method by which clinicians determine the initial filter density varies. Polling the clinicians on this study's planning committee indicated wide variability. Among the methods reported were 1) using a fixed density filter for all patients, 2) basing the density on visual acuity of the amblyopic eye, 3) using a Bangerter bar to increase filter density until the patient switches fixation, and 4) using different density filters for different patients but in somewhat of an arbitrary fashion based on the clinician's own previous clinical experience. Informal surveys administered during PEDIG investigator meetings held during the 2006 American Academy of Ophthalmology and the American Academy of Optometry annual meetings indicated that most clinicians use an empirical, rather than a customized methodology, to determine the initial Bangerter filter. In all cases, failure to improve was associated with the prescription of a more dense filter.

Bangerter filters may not degrade the visual acuity to the level labeled by the manufacturer, as suggested by pilot studies. In one study conducted by PEDIG investigators on 9 patients (2 teenagers and 7 adults) with normal visual acuity in each eye, the visual acuity was retested with Bangerter filters of 0.2, 0.1, and < 0.1 densities.[11] For the 0.2 filter used, which according to the manufacturer's label should reduce visual acuity to 20/100, the mean visual acuity was only reduced to 20/25. For both the 0.1 and <0.1 filters, which are designed to reduce visual acuity to 20/200 and 20/300 respectively, the mean visual acuity was only reduced to 20/50.[11] In contrast, another study of 20 adults with normal visual acuity in each eye reported a mean visual acuity reduction to 20/63, 20/250, and 20/125 for the 0.2, 0.1, and <0.1 Bangerter filters respectively.[12]

We speculate that the differences in visual acuity with the Bangerter filters may be due to the fact that similarly graded filters are not of uniform density.[13] There appear to be small clear areas in some filters, possibly allowing the patient to search for an area where they see best. If clear or reduced density areas do exist, it is not known to what extent this would be expected to affect the treatment benefit of Bangerter filters.

Few data are available comparing Bangerter foils with patching for the treatment of amblyopia. Bonsall[14] randomized 14 patients, 3 to 10 years old, with previously untreated strabismic/anisometropic amblyopia to either 6 hours of daily patching or full-time Bangerter foils.

Baseline amblyopic eye acuity was 20/30 to 20/400 for the patching group and 20/30 to 20/200 for the Bangerter group. The Bangerter foil prescribed was the minimum density foil needed to elicit a switch in fixation from the sound eye to the amblyopic eye. Visual acuity was measured every 6-8 weeks until the amblyopic eye visual acuity was equal to that of the sound eye, an improvement that was achieved in 5 of the 14 at the time the study was stopped. The average time to achieve equal vision between the amblyopic and sound eyes was about 4.5 months (142 days) for the foil group versus about 9 months (272 days) for the patching group. Both forms of therapy were equally tolerated. Despite good preliminary data, a large randomized clinical trial comparing the effectiveness of Bangerter filters with patching for the treatment of amblyopia has yet to be conducted.

1.2 Study Objectives

- Primary: To evaluate the non-inferiority of Bangerter filters to 2 hours of daily patching as a primary treatment for moderate amblyopia (20/40 – 20/80) in children ages 3 to <10 years.
- Secondary:
    - To determine the time course of visual improvement with Bangerter filter treatment.
    - To compare patient quality of life, measured by a modified Amblyopia Treatment Index, between patients treated with patching vs. Bangerter filters.
    - To determine whether the degree of blurring of sound eye visual acuity relative to the amblyopic eye visual acuity predicts improvement in acuity.
    - To determine whether fixation preference is predictive of improvement in visual acuity.

1.3 Synopsis of Study Design

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

- Age 3 to < 10 years
- Amblyopia associated with strabismus, anisometropia, or both
- No ocular cause apparent for reduced visual acuity
- Visual acuity 20/40 – 20/80 (71 to 54 letters inclusive) in amblyopic eye
- Visual acuity 20/40 or better (≥ 69 letters) in sound eye
- Interocular difference ≥ 3 logMAR lines (≥ 15 letters)
- No amblyopia treatment other than spectacles in last 6 months
- Currently wearing spectacles
- Appropriate spectacles have been worn for 16 weeks prior to enrollment or visual acuity documented to be stable
- No myopia > -6.00 D spherical equivalent in either eye
- Cycloplegic refraction within 6 months prior to enrollment

Treatment Groups

Patients will be randomized to two treatment groups:

- 2 hours daily patching of the sound eye plus one hour near activities while patching
- Bangerter filter worn on sound eye spectacle lens full time (0.3 for 20/40-20/63 and 0.2 for 20/80) plus at least one hour near activities

Sample Size

170 patients (85 per group) with moderate amblyopia (20/40 to 20/80)

Visit Schedule

- 6 weeks ± 2 weeks
- 12 weeks ± 2 weeks: Increase intensity of treatment if acuity not improved 1 line (5 letters) or more from baseline (*see section 3.4.2*)
- 18 weeks ± 2 weeks: Increase intensity of treatment if acuity not improved 2 lines (10 letters) or more from baseline and intensity of treatment not increased at 12 week visit (*see section 3.4.3*)
- 24 weeks ± 2 weeks: Primary outcome (masked exam)

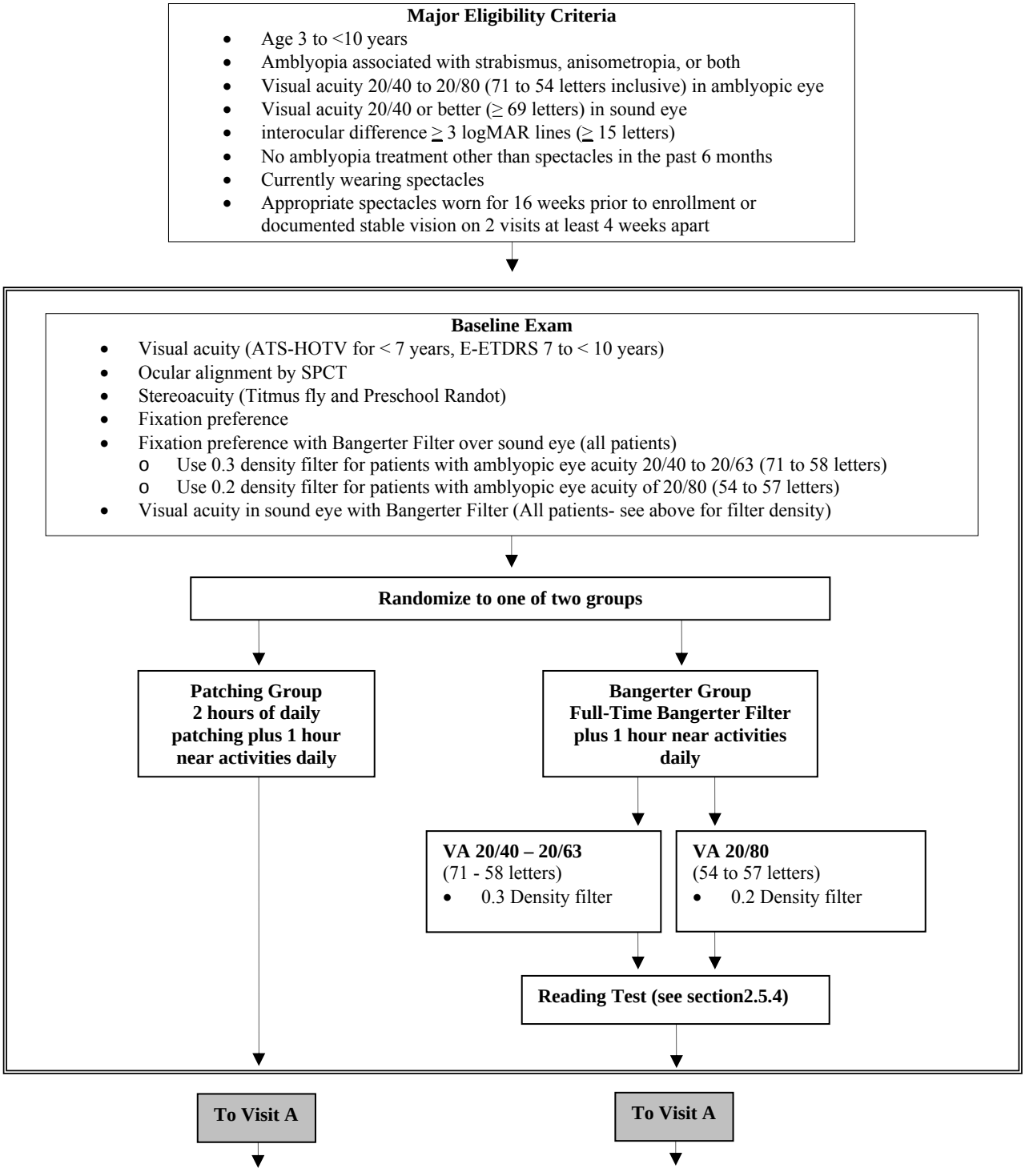
Primary Analysis

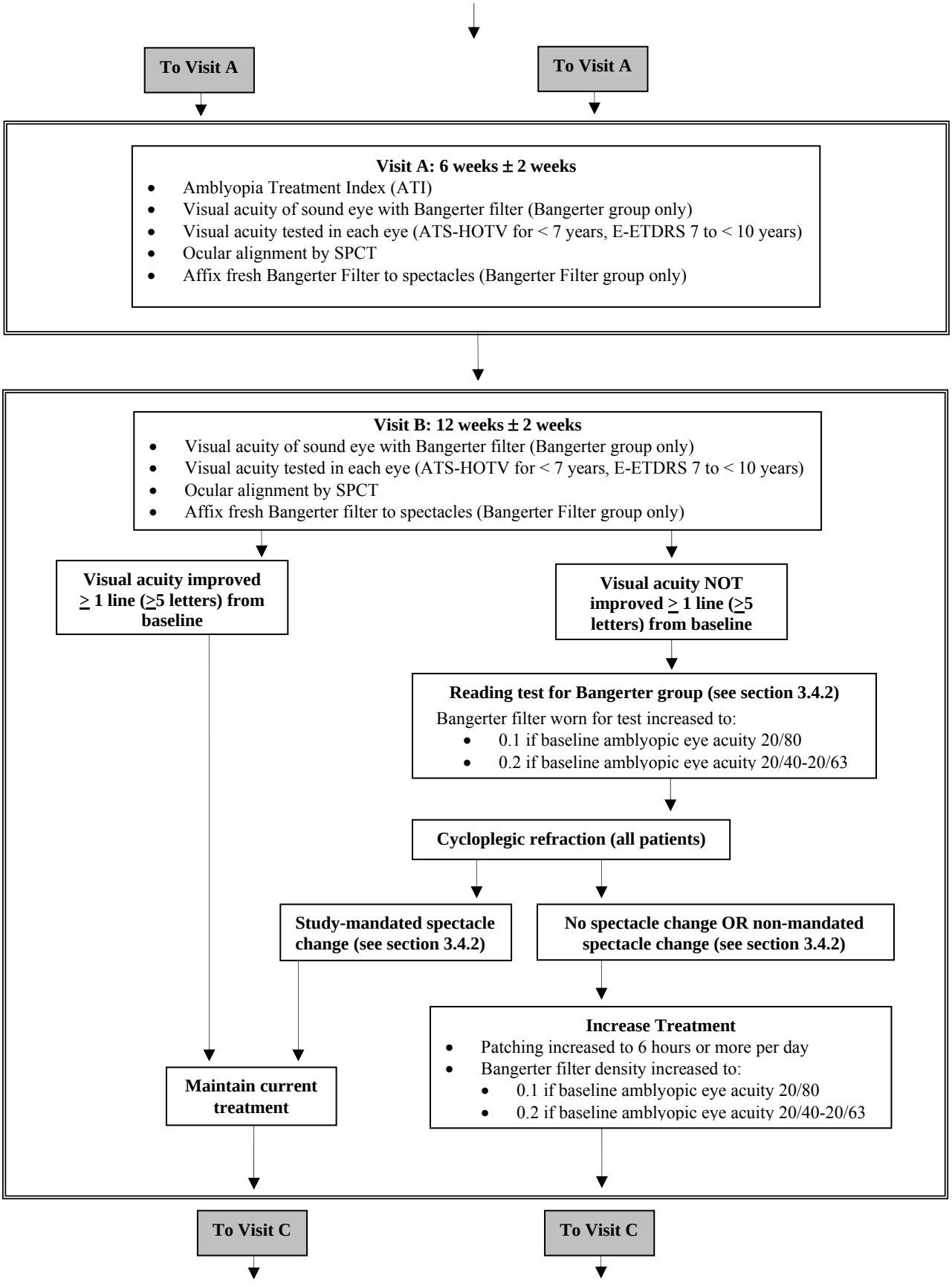
The primary outcome assessment is visual acuity at 24 weeks for both the amblyopic and sound eyes.

The primary analytic approach for the amblyopic eye acuity will involve construction of a one-sided 95% confidence interval to assess non-inferiority based on a treatment group comparison of logMAR visual acuity scores adjusted for baseline visual acuity scores in an analysis of covariance (ANCOVA) model.

Sound eye acuity data will be reported for each treatment regimen at the 24-week visit as mean change from baseline and as the distribution of the numbers of lines of change from baseline.

1.4 Study Summary Flow Chart




To Visit A
To Visit A
Visit A: 6 weeks ± 2 weeks
Amblyopia Treatment Index (ATI)
Visual acuity of sound eye with Bangerter filter (Bangerter group only)
Visual acuity tested in each eye (ATS-HOTV for < 7 years, E-ETDRS 7 to < 10 years)
Ocular alignment by SPCT
Affix fresh Bangerter Filter to spectacles (Bangerter Filter group only)
Visit B: 12 weeks ± 2 weeks
Visual acuity of sound eye with Bangerter filter (Bangerter group only)
Visual acuity tested in each eye (ATS-HOTV for < 7 years, E-ETDRS 7 to < 10 years)
Ocular alignment by SPCT
Affix fresh Bangerter filter to spectacles (Bangerter Filter group only)
Visual acuity improved ≥ 1 line (≥5 letters) from baseline
Visual acuity NOT improved ≥ 1 line (≥5 letters) from baseline
Reading test for Bangerter group (see section 3.4.2)
Bangerter filter worn for test increased to:
0.1 if baseline amblyopic eye acuity 20/80
0.2 if baseline amblyopic eye acuity 20/40-20/63
Cycloplegic refraction (all patients)
Study-mandated spectacle change (see section 3.4.2)
No spectacle change OR non-mandated spectacle change (see section 3.4.2)
Increase Treatment
Patching increased to 6 hours or more per day
Bangerter filter density increased to:
0.1 if baseline amblyopic eye acuity 20/80
0.2 if baseline amblyopic eye acuity 20/40-20/63
Maintain current treatment
To Visit C
To Visit C

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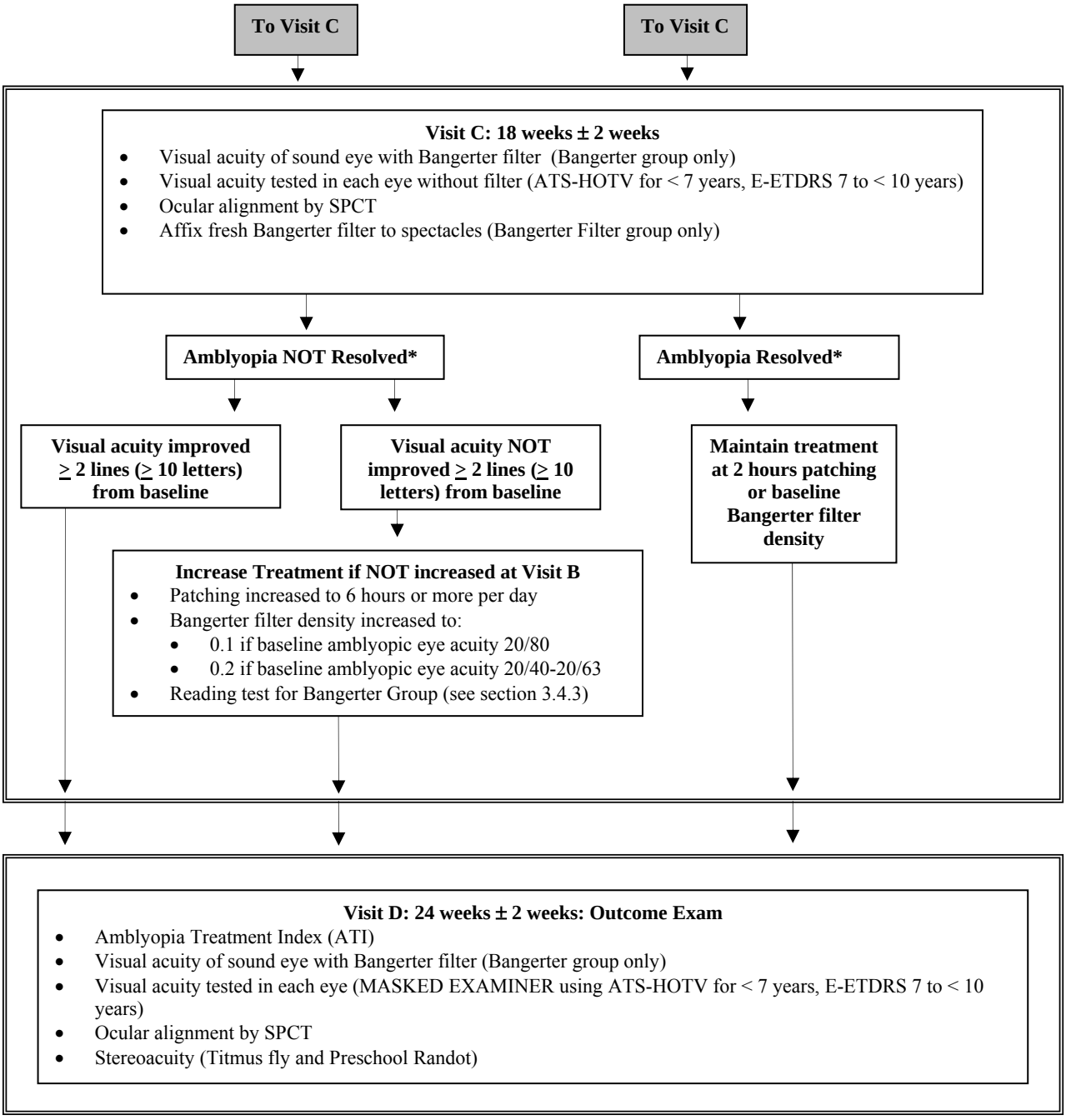

*Amblyopia resolved = Amblyopic eye acuity better than or equal to (<1 line or <5 letters) sound eye acuity

CHAPTER 2: PATIENT ENROLLMENT

2.1 Eligibility Assessment and Informed Consent

For patients who appear eligible for the study following a "standard-care" or preliminary examination, the study will be discussed with the child's parent(s) or guardian(s). Parent(s) or guardian(s) who express an interest in the study will be given a copy of the informed consent form to read. Written informed consent must be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the patient's routine care.

2.2 Eligibility and Exclusion Criteria

1. Age 3 to < 10 years

2. Amblyopia associated with strabismus (comitant or incomitant), anisometropia, or both
   - Criteria for strabismus: At least one of the following criteria must be met
     - Heterotropia at distance and/or near fixation on examination (with or without spectacles)
     - History of strabismus surgery (or botulinum)
     - Documented history of strabismus which is no longer present (and which, in the judgment of the investigator, is the cause of amblyopia)

   - Criteria for anisometropia: At least one of the following criteria must be met:
     - ≥0.50 D difference between eyes in spherical equivalent
     - ≥1.50 D difference between eyes in astigmatism in any meridian

3. Visual acuity, measured using the ATS single-surround HOTV protocol for patients aged < 7 years and the E-ETDRS protocol for patients 7 to < 10 years using the Electronic Visual Acuity Tester (the protocol for conducting the visual acuity testing is described in the *ATS Visual Acuity Testing Procedures Manual),* meeting the following criteria:
   - Best-corrected visual acuity in the amblyopic eye 20/40 to 20/80 inclusive (71 to 54 letters inclusive)
   - Best-corrected visual acuity in the sound eye ≥20/40 (≥ 69 letters)
   - Inter-eye acuity difference ≥3 logMAR lines (i.e., amblyopic eye acuity at least 3 lines by ATS-HOTV or at least 15 letters by E-ETDRS worse than sound eye acuity)

4. No amblyopia treatment other than spectacles in the past 6 months.
   - Any treatment more than 6 months prior to enrollment is acceptable

5. Spectacles must be worn currently

6. Spectacle correction for measurement of enrollment VA 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 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 in the spectacle lenses in both eyes must be within 6 degrees of the axis of the cycloplegic refraction when cylinder power is ≥ 1.00 D
- Myopia of the 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, or

2) until visual acuity in amblyopic eye is stable (defined as two consecutive visual acuity measurements by the same testing method at least 4 weeks apart with no improvement of one 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 first measurement. *Note: since this determination is a pre-study procedure, the method of measuring visual acuity is not mandated.*

7. No current vision therapy or orthoptics
8. No ocular cause for reduced visual acuity
9. Cycloplegic refraction within 6 months prior to enrollment
10. Ocular examination within 6 months prior to enrollment
11. No myopia more than –6.00 D spherical equivalent in either eye
12. No prior intraocular or refractive surgery
13. No known skin reactions to patch or bandage adhesives
14. Parent has home phone (or access to phone) and is willing to be contacted by the Jaeb Center.
15. Parent does not anticipate relocation outside area of an active ATS site within the next 6 months
16. Parent understands protocol and, if child is eligible to enter randomized trial, parent is willing to accept randomized treatment

2.3 Historical Information

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

2.4 Clinical Testing for Enrollment

Examination procedures include:

1. Measurement of visual acuity in each eye (right eye first) by the ATS single-surround HOTV for patients aged < 7 years and the E-ETDRS testing protocol for patients 7 to < 10 years using the Electronic Visual Acuity Tester. Aspects of the testing protocol that are specific to this study are indicated below:
   - Testing must be done without cycloplegia (with spectacles) no more than 7 days prior to randomization.
   - Since the patient needs to be wearing spectacles that provide best visual acuity to be enrolled, trial frames/phoropter with a different correction cannot be used to measure acuity at enrollment.
   - 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
   - If performed within prior 7 days, does not need to be repeated at time of enrollment
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. 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
5. Stereoacuity testing (prior to cycloplegia): Titmus fly, Randot Preschool Stereoacuity test
6. Fixation preference measured (prior to cycloplegia) by the PEDIG fixation preference test, according to the methods outlined in the *ATS Miscellaneous Testing Procedures Manual* and in the following manner:
   - Without a Bangerter filter
   - With a Bangerter filter. The filter density is selected based on visual acuity of the amblyopic eye (0.3 for 20/40 to 20/63 (71 to 58 letters) and 0.2 for 20/80 (54 to 57 letters)). The appropriate density filter trimmed roughly to the size of the average child's lens should be applied to the inner surface of the spectacle lens over the sound eye. This filter must be removed and may be used for measuring fixation preference in subsequent patients as long as it is stored on its original paper backing and remains clean. The filter is applied for the fixation preference test according to methods outlined in the *Bangerter application (short-term)* section of the *Bangerter Filter Application Procedures Manual* – This filter must not remain on spectacles following randomization (i.e., this filter must not go home with the child).
7. Measurement of visual acuity in the sound eye with a Bangerter filter (*see #6 above*) by the ATS single-surround HOTV for patients aged < 7 years and the E-ETDRS testing protocol for patients 7 to < 10 years using the Electronic Visual Acuity Tester.

2.5 Randomization of Eligible Patients

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

Treatment must commence within 72 hours following randomization; therefore, a patient should not be randomized until both the investigator and parent are ready to start treatment.

The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by site and age (3 to < 7 years, 7 to < 10 years), which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed.

2.5.1 Randomization Groups

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

1. 2 hours of daily patching combined with 1 hour of near visual activities while patching
2. Bangerter filter worn on sound eye spectacle lens full time (0.3 density for 20/40-20/63 (71 to 58 letters) and 0.2 density for 20/80 (54 to 57 letters)) combined with 1 hour of near visual activities.

2.5.2 Delay in Randomization

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

The ocular motility examination must be performed within 7 days prior to randomization. If patient randomization is delayed beyond 7 days, the ocular motility examination must be repeated.

No other parts of the examination (including the refraction) need to be repeated if they were performed within 6 months prior to randomization.

2.5.3 Bangerter Application

The Bangerter filter must be applied according to the methods for *Bangerter application (long-term)* outlined in the *Bangerter Filter Application Procedures Manual.*

2.5.4 Assessment of Reading Ability

Reading ability will be assessed binocularly prior to cycloplegia using the Grade-Level Reading Assessment Test in patients randomized to the Bangerter group after applying the Bangerter filter to the sound eye in patients aged 7 to <10 years. The patient may hold the reading card at any distance he or she finds comfortable.

Patients who (1) are unable to read the grade-appropriate sized print with the Bangerter filter over the sound eye and (2) will be attending school while on treatment will be prescribed separate glasses (single vision spectacles without Bangerter filter) to use for desk (near) work in school and home (paid for by the study). The time the patient wears the single vision spectacles without the Bangerter filter will be monitored by the parent.

CHAPTER 3: FOLLOW-UP AND TREATMENT

3.1 Treatment Groups

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

1. 2 hours of daily patching combined with 1 hour of near visual activities while patching
2. Bangerter filter worn on sound eye spectacle lens full time (0.3 density for 20/40-20/63 (71 to 58 letters) and 0.2 density for 20/80 (54 to 57 letters)) combined with 1 hour of near visual activities.

Spectacle wear will be continued as prescribed.

An instruction sheet specific to the randomized treatment group will be given to the parent at the time of randomization. This instruction sheet will explain the treatment to which the patient has been randomized and will include instructions for applying the patch and the Bangerter filter.

A calendar specific to the randomized treatment group will be given to the parent at the time of randomization. The parents will be instructed to record the total time the patch or the Bangerter filter was worn each day. Parents of children in the Bangerter group that receive glasses without the filter for school work will be instructed to record the total time the glasses without the filter are worn each day.

3.2 Near Visual Activities

For both treatment groups, the parent will be instructed to have their child spend 1 hour each day doing eye-hand coordination activities at near. For children in the patching group, this 1 hour must be during the period of time they are patched. For children in the Bangerter filter group, this may be performed at any time during the day while the child is wearing his/her spectacles and Bangerter filter.

An instruction sheet will be given to the parent which will indicate the types of near visual activities the child should do. Examples of activities include crafts, coloring, tracing, cutting out objects, blocks, Lego blocks, marbles, dominoes, card games, board games, puzzles, written homework assignments, sorting or stringing beads, reading, writing, activity books, dot-to-dot connecting, hidden pictures, word finds, and computer or video games (e. g., Game Boy/Nintendo/ PlayStation).

3.3 Follow-up Visit Schedule

All patients will have the following study visits after randomization:

- Visit A: 6 weeks ± 2 weeks
- Visit B: 12 weeks ± 2 weeks
- Visit C: 18 weeks ± 2 weeks
- Visit D: 24 weeks ± 2 weeks

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

3.4 Testing Procedures

The following testing will be performed at follow-up visits:

1. Measurement of sound eye visual acuity through the filter for patients in the Bangerter group by the ATS single-surround HOTV protocol for patients aged < 7 years and the E-ETDRS protocol for patients 7 < 10 years using the Electronic Visual Acuity Tester. The same visual acuity protocol used at baseline must be used for all subsequent exams (e.g., if a patient is tested with the HOTV protocol at the baseline exam, visual acuity must be measured by the HOTV protocol on all subsequent exams whether or not the patient is 7 years or older at subsequent exams.)
2. Measurement of visual acuity in each eye (right eye first) by the same visual acuity testing method described above *(see #1)*
    - Testing is performed without cycloplegia with spectacles and without the Bangerter filter
3. Ocular alignment measured with the SPCT
4. Titmus fly and Randot Preschool Stereoacuity test at the 24-week visit only. Testing must be done in spectacles after removal of the Bangerter filter.

3.4.1 Visit A: 6 weeks ± 2 weeks

- Administration of the Amblyopia Treatment Index (ATI) prior to visual acuity measurement
- Assessment of sound eye visual acuity through the Bangerter filter (Bangerter group only)
- Assessment of visual acuity in both eyes without filters (spectacles must be cleaned)
- Ocular alignment: record alignment measurements by SPCT
- Replace Bangerter filter with same intensity filter as worn at enrollment. The filter should be applied according to the methods for ***Bangerter application (long-term)*** outlined in the *Bangerter Filter Application Procedures Manual*

3.4.2 Visit B: 12 weeks ± 2 weeks

- Assessment of sound eye visual acuity through the Bangerter filter (Bangerter group only)
- Assessment of visual acuity in both eyes without filters and prior to cycloplegia (spectacles must be cleaned). If testing indicates that amblyopia has resolved (amblyopic eye acuity equal to or better than sound eye acuity, i.e., <1 line or <5 letters), treatment will be maintained at the current level.
- Ocular alignment by SPCT
- Reading test for patients 7 to <10 years old in the Bangerter treatment group who have failed to improve 1 line (5 letters) or more from baseline. For this test, patients must wear a Bangerter filter with the next density increment from what is currently worn (0.2 density filter if currently wearing a 0.3 density filter, or 0.1 density filter if currently wearing a 0.2 density filter). The appropriate density filter trimmed roughly to the size of the average child's lens should be applied to the inner surface of the spectacle lens over the sound eye. This filter must be removed and may be used for measuring fixation preference in subsequent patients as long as it is stored on its original paper backing and remains clean. This filter must not remain on spectacles following the reading test (i.e., this filter must not go home with the child).
- Mandatory cycloplegic refraction for all patients (regardless of treatment group) failing to improve 1 line (5 letters) or more from baseline. If current spectacles do not meet the following criteria, new lenses must be prescribed:

1. Spherical equivalent must be within 0.50 D of fully correcting the anisometropia
2. Hypermetropia must not be undercorrected by more than +1.50 D spherical equivalent
3. Cylinder power in both eyes must be within 0.50 D of fully correcting the astigmatism
4. 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
5. Myopia 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

- The cost of this mandatory lens change will be covered by the study.
- If a lens change is mandated, the patient is not eligible for increasing treatment until Visit C, and continues treatment as currently prescribed.
- Optional lens changes may be made at the discretion of the investigator if the results of the cycloplegic refraction do not mandate a lens change based on the criteria above. The cost of this optional change in lenses will not be covered by the study.

- Increase treatment intensity if no improvement in visual acuity of 1 line (5 letters) or more from baseline (unless a spectacle change is mandated for the patient following the mandatory cycloplegic refraction –*see above*):
  - For eyes in patching group that have not improved by at least 1 line (5 letters) from baseline, patching will be increased to 6 or more hours per day
  - For eyes in the Bangerter filter group that have not improved at least 1 line (5 letters) from baseline, the filter density will be increased to 0.2 for patients with baseline visual acuity of 20/40 – 20/63 (71 to 58 letters) and increased to 0.1 for patients with baseline visual acuity of 20/80 (54 to 57 letters).
  - If treatment intensity is increased for patients in the Bangerter filter group and the patient was determined to have problems reading age-appropriate text on the reading test performed at the time of the 12-week study visit, a separate pair of glasses (single vision spectacles without Bangerter filter) for school work will be prescribed for use at desk (near) work in school and home (*as described in section 2.5.4*).
- Replace Bangerter filter with same intensity filter as Visit A if not increasing intensity of treatment. Otherwise, affix increased intensity filter. The filter should be applied according to the methods for ***Bangerter application (long-term)*** outlined in the *Bangerter Filter Application Procedures Manual.*

3.4.3 Visit C: 18 weeks ± 2 weeks

- Assessment of sound eye visual acuity through Bangerter filter (Bangerter group only)
- Assessment of visual acuity in both eyes without filters (spectacles must be cleaned). If testing indicates that amblyopia has resolved (amblyopic eye acuity equal to or better than sound eye acuity, i.e., <1 line or <5 letters), treatment will return to the original level of treatment prescribed at randomization.
- Ocular alignment by SPCT.
- Increase treatment intensity if no improvement in visual acuity AND no increase of treatment intensity at visit B:

- For eyes in patching group that have not improved at least 2 lines (10 letters) from baseline, patching will be increased to 6 or more hours per day.
- For eyes in the Bangerter filter group that have not improved at least 2 lines (10 letters) from baseline, the filter density will be increased to 0.2 for patients with baseline acuity of 20/40 – 20/63 (71 to 58 letters) and increased to 0.1 for patients with baseline acuity of 20/80 (54 to 57 letters).
- If treatment intensity is increased, an age appropriate reading test for patients 7 to <10 years old will be performed as in *section 2.5.4* and separate glasses (single vision spectacles without Bangerter filter) for school work prescribed if needed for patients in the Bangerter filter group.

- Replace Bangerter filter with same intensity filter as Visit B if not increasing intensity of treatment. The filter should be applied according to the methods for ***Bangerter application (long-term)*** outlined in the *Bangerter Filter Application Procedures Manual.*

3.4.4 Visit D: 24 weeks ± 2 weeks – Primary Outcome Exam

- Administration of the Amblyopia Treatment Index (ATI) prior to visual acuity measurement
- Assessment of sound eye visual acuity through the Bangerter filter (Bangerter group only)
- Masked assessment of visual acuity in both eyes without filters (spectacles must be cleaned)
- Ocular alignment by SPCT
- Assessment of binocular function by stereoacuity testing:
  - Bangerter filter must be removed
  - Titmus Fly test and Randot Preschool Stereoacuity test

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS

4.1 Management of Optical Correction

A refraction should be performed whenever the investigator suspects that refractive error may not be optimally corrected.

4.2 Management of Strabismus

Strabismus surgery is allowed at the discretion of the investigator. Surgery will be recorded in the comment section of the Follow-up Examination Form.

4.3 Worsening of Visual Acuity in the Amblyopic Eye

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

4.4 Patient Withdrawals

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

4.5 Risks

There are no risks involved in this study that would not be part of usual care.

4.5.1 Risks of Examination Procedures

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

4.5.2 Risk of Patching

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

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.

Patching potentially could decrease the visual acuity in the sound eye, although this is almost always reversible. However, this occurrence is extremely unlikely in view of 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 an ocular deviation, although this has been found to be very rare in our previous studies and indistinguishable from the natural history of the condition. If treatment precipitates the development of an ocular deviation (e.g., esotropia in child with hyperopia), the parent will be advised to have the patient see the investigator as soon as possible.

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

4.5.3 Risk of Bangerter Filters

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

The more dense Bangerter filters potentially could decrease the visual acuity in the sound eye, although this is almost always reversible. However, this occurrence has not been reported. The diagnosis and management of reverse amblyopia is left to the investigator's judgment.

There are some activities that may require extra caution when using the Bangerter filter due to the level of vision in the amblyopic eye and blurring in the sound eye. These activities include riding a bike, in-line skating, and skateboarding. The consent form will instruct parents that the child may require more supervision when performing these activities.

4.6 Reporting of Adverse Events

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

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

4.7 Patient Payments

The parent/guardian of each patient will be compensated $25 for completion for each protocol-specified follow-up visit to a maximum of $100. If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses. All payments will be made by the Jaeb Center by the month following the date of each completed visit.

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 patients.

4.9 Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. The Jaeb Center staff will be contacting the parent/guardian by phone to facilitate visit scheduling. A patient newsletter and study updates may be sent. Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients.

CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The estimation of sample size and statistical analysis plan are summarized below and detailed in separate documents. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in *section 5.2* contains the framework of the anticipated final analysis plan, which will supersede *section 5.2* when it is finalized.

5.1 Sample Size Estimation

The sample size estimate has been computed for the primary study objective, to determine whether the visual acuity improvement at 24 weeks obtained with Bangerter filters is at least as good (noninferior) as the improvement obtained with patching, in concert with the analytic approach for this objective (analysis of covariance) as described in *section 5.2*.

Based on data from previous ATS studies (ATS1, ATS2, ATS3, and ATS5), we assumed a standard deviation for the 24-week outcome score of 0.16 logMAR and a correlation between baseline and 24-week outcome score of 0.20.

To select a sample size for this trial, it is necessary to set the non-inferiority limit, which represents the end of a 95% confidence interval for the difference in mean acuity between groups. A limit of 0.075 logMAR (3.75 letters) was considered by the Planning Committee to provide sufficient evidence for non-inferiority. Because the primary objective is to determine whether Bangerter filters are as effective as patching, non-inferiority of the Bangerter filters will be declared if the upper limit of a 1-sided 95% confidence interval constructed on the difference between adjusted mean visual acuity scores for the two groups (Bangerter filter – Patching) is less than the specified non-inferiority limit.

For a 0.075 logMAR non-inferiority limit, a 1-sided 95% confidence interval, 90% power, a standard deviation of 0.16 logMAR and correlation between the baseline and outcome acuities of 0.20, the sample size of moderate amblyopes required for the study was estimated to be 152, equally divided between the two groups. This was increased to 170 to account for up to 10% loss to follow-up.

5.2 Primary Analysis

Non-inferiority of the Bangerter filters will be declared if the upper limit of a 1-sided lower 95% confidence interval constructed on the difference between adjusted mean visual acuity scores for the two groups (Bangerter filter – Patching) is less than the specified non-inferiority limit of 0.075 logMAR.

The adjusted means mentioned above will be obtained through application of an Analysis of Covariance (ANCOVA) model using baseline visual acuity scores as the covariate and 24-week visual acuity scores as the dependent variable. A 1-sided confidence interval will be formed on the difference between 24-week visual acuity mean scores after these means have been adjusted for the baseline acuity scores.

The primary analysis approach will be developed in conjunction with the DSMC.

5.3 Secondary Analyses

5.3.1 Time Course of Visual Acuity Improvement with Bangerter Filters

A secondary analysis will be performed to determine the time course of visual acuity improvement with Bangerter Filters and compare this improvement with the time course of visual acuity improvement with patching.

A Cox proportional hazard model will be used to compare the time until visual acuity improvement across treatment groups, adjusting for baseline visual acuity. Visual acuity improvement will be measured as time to 20/25 or better visual acuity of the amblyopic eye

A random effects model will be used to compare time to visual acuity improvement. A regression line for each individual will be fit for visual acuity over time. Then the average slope in the Bangerter filter group will be compared to the average slope in the patching group.

A population-averaged model will also be used to compare time to visual acuity improvement. The average visual acuity at each time point will be calculated for the Bangerter filter and patching groups separately. Then a regression line will be fit for the mean visual acuity in each treatment group over time, and the slopes of these lines will be compared. A comparison of mean visual acuity by treatment at each time point also will be performed by fitting a discrete time model and using linear contrasts.

Prior to performing the random effects or population-averaged mixed model analysis, exploratory analyses will be performed to determine the time course of improvement in visual acuity over time and the correlation structure of the data. These will be used (1) to guide choice of the correlation structure for the population-averaged model and (2) determine whether data transformation is needed to linearize the relationship between time and visual acuity improvement.

5.3.2 Impact on Quality of Life

A secondary analysis will be a treatment group comparison of scores obtained on the modified Amblyopia Treatment Index (ATI) 24 weeks after randomization. Given that the questionnaire will have been modified, the first step will be to conduct a factor analysis to confirm whether the same factor structure still applies. Assuming the same factors are confirmed, the average of the item responses over each factor will be calculated and compared by treatment group with a t-test for difference in means.

5.3.3 Predictive Value of Blur

A secondary analysis will be performed, limited to patients in the Bangerter filter group, to determine whether blurring the sound eye visual acuity with Bangerter filters is predictive of visual acuity improvement. The amount of blur will be explored in two ways:

- a continuous measure of the degradation in sound eye acuity with the filter
- a dichotomous variable indicating if sound eye acuity with the filter is worse than the amblyopic eye acuity.

Descriptive data and simple linear regression models will be used to explore the relationship between blur measured at each follow-up visit and the corresponding change in amblyopic eye visual acuity from the previous visit, adjusting for the amount of blur at the previous visit. If the estimated effect of blur looks consistent, a longitudinal model with both measures of blur as time dependent covariates will be used.

5.3.4 Predictive Value of Fixation Preference

A secondary analysis will be performed, limited to patients randomized to the Bangerter filter group, to determine whether a change in fixation preference is predictive of visual acuity improvement in patients with amblyopia. Two variables will be created:

- Fixation preference with the Bangerter filter
- Switch in fixation preference – in which possibilities for the data are all combinations of fixation preference with and without the Bangerter filter.

Descriptive data will be used to explore the relationship between fixation preference and change in amblyopic eye visual acuity, and any further analysis will be decided once the distribution of the data is determined.

5.3.5 Subgroup Analysis

The treatment effect in subgroups based on baseline factors will be assessed. The subgroups of interest are those based on baseline visual acuity, cause of amblyopia, age, and prior treatment. For determining cause of amblyopia for analysis purposes, amblyopia associated with strabismus or with anisometropia will be defined as explained in *section 2.2 #2*. Combined mechanism amblyopia will be defined using the following criteria:

- Both of the following criteria must be met:
  - Criteria for strabismus are met (*see section 2.2 #2*)
  - ≥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.*

CHAPTER 6: REFERENCES

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