INTERMITTENT EXOTROPIA STUDY 6 (IXT6)

A Pilot Randomized Clinical Trial of Base-in Prism Spectacles for Intermittent Exotropia

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. It is one of a series of randomized trials and observational studies conducted by PEDIG that address management of intermittent exotropia (IXT) in children.

1.1 Intermittent Exotropia

The most common type of childhood-onset exotropia is IXT,[1-4] with a reported incidence of 32.1/100,000,[1] occurring more frequently in females[5] and in Asian children.[4, 6, 7] IXT is a term used to describe several subgroups of intermittent exodeviations, namely basic, true divergence excess, pseudo divergence excess, and convergence insufficiency IXT. Many cases of exodeviations are characterized by an exotropia that occurs primarily for distance viewing, but may also be present at near. Normal binocular single vision and normal stereoacuity are usually present at near when the exotropia is controlled, although stereoacuity can be reduced in about 25% of cases.[8, 9]

The current management of IXT includes observation as well as surgical and non-surgical interventions.[8] Many practitioners treat IXT patients using non-surgical approaches such as part-time patching, over-minus lenses, vision therapy[10, 11] or prism.[12, 13]

1.2 Prism Treatment for IXT

One non-surgical treatment for IXT is base-in corrective or relieving prism,[14, 15] which eliminates or reduces the convergence demand, respectively. Corrective prism is a term used when the full angle of deviation is corrected with prism while relieving prism provides prism correction less than the full angle of deviation. Although corrective base-in prism for IXT has been reported to have a favorable treatment benefit in two small retrospective studies,[12, 13] its clinical effectiveness (either using corrective or relieving prism) has not yet been studied prospectively in either randomized or non-randomized controlled trials.

1.3 Previous Studies of Prism Therapy for IXT

While many studies have reported use of prism as part of a multi-faceted non-surgical treatment approach and adjunct to surgical treatment of strabismus in general, we are aware of only two small studies that have evaluated corrective prism alone as an intervention specifically for IXT:

Pratt-Johnson and Tillson 1979[12]

Twenty-five children (aged 2-8 years) with small-angle (<20Δ) IXT were evaluated retrospectively, 13 of whom had undergone previous surgery but had residual or recurrent IXT. Spectacles were prescribed with base-in prism (typically Fresnel Press-On prism that was generally split evenly between the eyes) that fully corrected the maximum angle of deviation. Six of 25 never obtained their prism spectacles and 7 of 25 wore them < 50% of the time, and these patients (total n=13) were used as a pseudo-control group. The other 12 patients wore their prism spectacles >50% of awake hours for 12 months to 2.5 years (8 of 12 had undergone previous surgery). Prism was discontinued for 1 month and outcomes were evaluated.

The outcome was "cure," defined by the authors as meeting all of the following criteria: 1) no monocular eye closure in sunlight; 2) no manifest tropia at any distance; 3) 40 arc secs of stereopsis on the Wirt test; 4) divergence amplitudes ≥ 5Δ on the synotophore (major

amblyoscope) using a foveal fusion target; 5) recognition of diplopia immediately when the divergence amplitude was exceeded; 6) good convergence amplitude; and 7) total convergence and divergence amplitudes > 20Δ in the synotophore (major amblyoscope) or in free space with prisms.

Results: Eight of 12 patients (67%) in the prism group met criteria for cure (2 of 4 with previously un-operated IXT and 6 of 8 with previously operated IXT). None of the 13 patients in the pseudo control group met criteria for cure. However, it is important to recognize that this was not a true control group, and it is unknown if additional clinical factors were present that limited patient compliance.

Véronneau-Troutman et al 1976[13]
The authors retrospectively evaluated 14 patients (average age of 8.3 years; range 3 to 26 years) with IXT (mean angle of deviation 26.4Δ, range 12-45Δ), treated with Fresnel prisms (fully correcting the average of distance and near horizontal deviation plus any vertical). Average duration of treatment was 3.7 months and outcomes were assessed out of prism (time out of prism not provided).

Results: Control of the IXT was reported to be improved (some changed from constant XT to either IXT or exophoria, some changed from IXT to exophoria), the angle of deviation decreased on average by 4.6Δ, and mean convergence amplitudes improved by 6.2Δ at distance and 9.3Δ at near.

While the prism amounts prescribed in the aforementioned studies were fully "corrective" (prism power equaled the exodeviation angle), it was stated that the prism amount was often a mean of near and distance deviations.

In contrast to fully corrective prism, Vérnonneau-Troutman subsequently suggested in her textbook on prisms that "the *minimum* power necessary to achieve control of the exodeviation at distance" should be prescribed.[16] Others also recommend that the minimum "relieving" prism that provides improved sensorimotor fusion (e.g., control, suppression, stereopsis) be prescribed.[14, 15]

1.4 Possible Mechanisms of Prism Therapy

Whether relieving or correcting prism is used, the mechanism for improvement of IXT with prism therapy is largely unknown. In the short term, prism may improve the ability of the child to control the exodeviation by reducing or eliminating the fusional convergence demand necessary to align the eyes (less convergence is required for bifoveal stimulation with the prism than without). In the longer term, prism therapy for IXT may benefit the individual by increasing the time of fusion and perhaps weakening suppression, leading to an improvement in the ability to control the exodeviation.[12] The majority of patients with IXT typically have normal sensory fusion and reduced compensating fusional convergence ability,[14-16] and therefore the adage that "sensory fusion is the best orthoptics" forms the basis for this treatment; the anticipation is that better sensory fusion will encourage the development of better motor control.[17]

1.5 Methods of Prescribing Prism for IXT

There is currently no universally accepted formula or method for determining the optimal prism treatment for patients with IXT. The amount of prism prescribed to treat IXT in previous studies and in clinical practice varies and is based on 3 philosophical approaches:

1. Corrective prism is prescribed for the full angle of deviation.
2. Customized prism: the minimum prism required to comfortably improve fusion (e.g., better control, change of diplopia or suppression response to a fusion response on testing, decrease in the frequency of the IXT based on cover-uncover testing). This approach could result in corrective or relieving prism being prescribed, albeit for IXT, the customized approach usually results in relieving prism and rarely in corrective prism.
3. A fixed amount of relieving prism (e.g., always prescribe 5Δ or 10Δ) or a prism magnitude that is a percentage of the maximum exodeviation: The percentage of the deviation to correct is typically 33% to 50% of the maximum deviation[18] and is usually divided equally between the two eyes.[14, 18]

Regardless of which method is used to determine the amount, prism can be prescribed by adding Fresnel Press-On prism to spectacles or grinding prism into the lenses, Although Fresnel prism is a treatment option, most patients prefer ground-in prism because of better cosmetic appearance and improved clarity of vision.

1.6 Potential Problems with Prescribing Corrective Prism

Corrective prism is typically prescribed by dividing the total prism deviation and placing half as base-in prism in front of each eye to encourage bifoveal fusion. Despite these attempts to induce bifoveal stimulation, one can argue that this situation may not be ideal for patients who continue to suppress when fully aligned. In such cases, it is possible that the prisms either would have no benefit to the long term improvement of control of the IXT or prism adaptation could occur.[18] Additionally, the use of corrective prism is less practical in larger deviations as more optical aberrations may occur with larger prism magnitudes, in addition to the spectacle lenses being larger and heavier.

1.7 Potential Problems with Prescribing Customized Prism

Another approach to prescribing prism for treatment of IXT is a customized approach, where the amount of base-in prism to prescribe is the minimum amount of prism that is required to comfortably improve some aspect of sensorimotor fusion (e.g., better control, change of diplopia or suppression response to a fusion response on testing, decrease the frequency of the IXT based on cover-uncover testing, increase in stereoacuity) as determined by testing in the office. Because of the variable nature of IXT, the amount of prism magnitude needed for an individual patient might vary from one moment to another. In addition, this approach is quite dependent on the subjective interpretation of the examiner. Finally, prism adaptation could occur for relieving prism as well, thus increasing the magnitude of the deviation. For these reasons, a customized method of prescribing prism for IXT is not conducive to a standardized study protocol.

1.8 Prism Adaptation

Prism adaptation is a term that describes sensorimotor adaptation to prism treatment and can be part of the normal vergence system.[19] However, when prisms are placed to correct the angle of deviation in some patients, especially with acquired esotropia, the patient “adapts” to the prism in place, thus effectively making the deviation larger. The Prism Adaptation Study demonstrated greater surgical success in patients with acquired esotropia when the larger, prism-adapted, angle was targeted for surgery.[20]

This same phenomenon has been observed clinically in other types of strabismus as well. It is possible that patients with IXT could prism adapt to a larger angle when base-in prism is used as treatment for IXT. Because the proposed benefit of prism therapy for IXT is increased time of bifoveal fusion, patients who fully prism-adapt to the prescribed base-in prism (no improvement in the angle with the prism in place), would not be expected to have any treatment benefit, and so will be excluded in this study. Whereas patients who do not prism-adapt, or only partially prism-adapt (a smaller residual angle in prism, compared with before prism), are hypothesized to improve.

1.9 Determining the Dose of Prism for the Current Study

The consensus of the Planning Committee was to prescribe relieving prism. This decision was based primarily on the clinical experience of the Planning Committee. Consensus was reached to prescribe a base-in prism magnitude that was 40% of the largest exodeviation at distance or near for a maximum eligible exodeviation of 35Δ at both distance and near. This amount of relieving prism was determined based on Caloroso's residual vergence demand guidelines,[14] prism guidelines from Roper-Hall,[18] and expert opinion. Given the maximum deviation of 35Δ, the largest magnitude of prism to be prescribed will be 14Δ (7Δ for each eye). This magnitude of ground-in prism was agreed to be feasible in terms of appearance, weight, and optical aberrations. The minimum prism dose would be 6Δ (3Δ for each eye) based on the study-defined exodeviation of at least 16Δ at distance.

1.10 Public Health Importance of Proposed Randomized Clinical Trial

Although prism treatment for IXT is used in clinical practice by some eye care providers, there have been no randomized clinical trials evaluating its effectiveness. If prism treatment can successfully restore binocular alignment and facilitate improved control of the IXT without the need for surgery or office visits for other treatments, there potentially would be a significant cost savings. On the other hand, evidence that prism treatment for IXT is not effective would reduce the utilization of this treatment, allowing children to receive more effective treatments with less delay and avoiding the cost of unnecessary glasses.

1.11 Questions Related to Prism Therapy

There have been no rigorous studies that address the following important questions related to prism therapy:

1. Does prism therapy have an initial short-term therapeutic effect on IXT while wearing prism (over a number of weeks)?
2. Does prism therapy continue to have a long-term therapeutic benefit for IXT while wearing prism spectacles (over many months or years)?
3. Does prism therapy have a long-term therapeutic effect for IXT when prism spectacles are tapered and discontinued?

In the initial planning stages of the study we considered a full-scale RCT to address these questions, likely comparing prism therapy to non-prism spectacles. On further discussion, it became apparent that the lack of published data using relieving prism therapy lends itself to the need for a pilot study to answer question 1 prior to moving forward with questions 2-3. As a first step, we determined that a pilot study was needed to evaluate whether there is a short-term therapeutic treatment effect while wearing base-in relieving prism over a period of weeks, noting

that if there is not a treatment effect in the short-term, then a long-term benefit would not be expected.

1.12 Definitions of Treatment Response

Previous PEDIG studies have used a "control score" (the proportion of time that the deviation is manifest) to judge improvement or worsening of IXT or response to treatment.[21-24] A single control score has been found to be highly variable.[25 26] Due to this variability, a more adequate representation of control during the day can better be achieved by measuring the "triple control score,"[26] which is a mean of 3 control measures obtained at various times during an examination.

Because the purpose of the treatment of IXT with prism spectacles is to better align the eyes for a greater proportion of time, and single binocular vision with high grade stereoacuity is associated with good ocular alignment, it is reasonable to primarily focus on "control" of the distance deviation as the first step in evaluating the effectiveness of prism treatment as in prior overminus studies (IXT3, IXT5).[23]

1.13 Timing of Intervention, Outcome for Current Study

To evaluate the initial response to prism spectacles, this 8-week pilot randomized clinical trial (RCT) is proposed. If a reasonable initial response without significant adverse effects is found, a subsequent full-scale RCT would evaluate the long-term effectiveness of prism (e.g., over 1 year) and then evaluate the subsequent effectiveness of maintaining control after the prism treatment has been discontinued (e.g., 6 months after discontinuation of prism). This approach was successfully used previously to explore overminus spectacles as a treatment for IXT through an 8-week pilot RCT (IXT3), followed by a full-scale longer RCT to evaluate the long-term effectiveness on treatment and after discontinuation of treatment (IXT5).

1.14 Study Objective

The objective of this short-term, pilot randomized trial comparing spectacles with relieving prism to spectacles without prism is to determine whether to proceed to a full-scale, longer-term randomized trial. This decision will be based primarily on assessing the initial (8-week) response to prism by comparing treatment groups on the following outcomes:

- Mean distance IXT control score (the mean of 3 control scores) (primary outcome)
- The proportion of participants demonstrating a "treatment response," defined as ≥1 point improvement in the mean distance IXT control score without spontaneous exotropia during control testing (secondary outcome)
- The proportion of participants reporting adverse effects and good/excellent spectacle wear compliance

1.15 Synopsis of Study Design

Major Eligibility Criteria for Enrollment *(see section 2.2 for a complete listing)*

- Age 3 to < 13 years
- Intermittent exotropia meeting all of the following criteria:
    - Mean distance control score of ≥2.00 points with at least 1 measure of 3, 4, or 5 points (i.e, spontaneous tropia) from the 3 assessments during the exam
    - A near control score ≤4 on at least 1 of 3 assessments (cannot have score of 5, 5, 5)
    - Distance exodeviation between 16Δ and 35Δ (inclusive) by PACT
    - Near exodeviation between 10Δ and 35Δ (inclusive) by PACT

    - Near deviation does not exceed distance deviation by more than 10Δ by PACT (i.e., convergence insufficiency-type IXT excluded)
- No dissociated vertical deviation (DVD)
- No vertical deviation >3Δ in primary gaze at distance or near
- No patterns (such as an "A" or "V" pattern) with a downgaze measurement of >10Δ difference from straight ahead by PACT, measured per investigator's routine method
- No treatment for IXT or amblyopia (other than refractive correction) within the past 4 weeks, including vision therapy, orthoptics, patching, atropine, or other penalization
- No substantial overminus spectacles (spectacles overminused by more than 1.00D SE than the most recent cycloplegic refraction and ALSO results in minus SE power in the spectacles; underplussing is allowed) within the past 4 weeks
- No prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- No previous use of prism spectacles
- Refractive error between -6.00D spherical equivalent (SE) and +2.50D SE (inclusive) (*based on a cycloplegic refraction performed within 7 months but prior to the day of enrollment)*
- Refractive correction (must be worn for at least 1 week if refractive error meets any of the following (*based on a cycloplegic refraction performed within 7 months but prior to the day of enrollment)*:
    - SE anisometropia ≥1.00D
    - Astigmatism ≥1.00D in either eye
    - SE myopia ≥-0.50D in either eye
- If spectacles have been prescribed and are worn, they must meet the following pre-enrollment criteria:
    - SE anisometropia corrected to within 1.00D of full SE anisometropic difference
    - Astigmatism corrected to within 1.00D of full magnitude; axis within 10 degrees if astigmatism ≤1.00D and axis within 5 degrees if astigmatism >1.00D

<u>Additional Eligibility Criteria for Randomization Based on Prism Adaptation Testing</u>

- Exodeviation by PACT while wearing "trial" relieving prism for 30 minutes is smaller at distance or near than measured during initial testing (e.g. not fully adapting to prism at both distances)
- No new esotropia on cover test at near while wearing "trial" relieving prism for 30 minutes, compared with enrollment measurement taken without prism
- No esodeviation >6Δ on PACT at near while wearing "trial" relieving prism for 30 minutes

<u>Sample size</u>

Up to 100 participants will be enrolled for same-day prism adaptation testing until up to 64 participants meeting the randomization eligibility criteria based on the prism adaptation test are randomized (32 per treatment group).

<u>Treatment Groups</u>

Randomization (1:1) to the following groups:

- Prism Group: Spectacles with refractive correction AND base-in relieving prism (40% of the greater of the exodeviation by PACT at distance or near) equally divided between the 2 lenses

- Non-prism Group: Spectacles with refractive correction (or plano spectacles if no significant refractive error) and no prism

Visit Schedule

- Enrollment Visit
- If eligible, Randomization (same day as enrollment visit or within 7 days)
- 3-week phone call (21 to 28 days) after randomization
- Outcome Exam: 8 weeks (± 2 weeks) after randomization

Testing Procedures

Distance and near control of IXT (3 measurements), near stereoacuity, distance and near cover test, and distance and near PACT will be measured by a study-qualified examiner at enrollment, and by a Masked Examiner at 8 weeks. The prism adaptation test will be assessed by a study-qualified examiner at enrollment. Distance visual acuity, fusional convergence amplitude, and suppression will be assessed by a study-qualified examiner at both visits. In addition, symptoms of headache, eye strain, dizziness, nausea, and problems with spectacle wear will be assessed at both visits.

Primary Analysis

- A comparison of mean distance control scores (mean of 3 assessments over the exam) between the prism group and the non-prism group at 8 weeks.

Secondary Analyses

- A comparison of the proportion of participants showing a "treatment response," defined as an improvement of ≥1 point in distance control (mean of the 3 assessments over the exam) between enrollment and 8 weeks.
- A comparison of the proportion of participants showing no spontaneous tropia during control testing at the outcome exam.

Ancillary Screening Study/Analysis

- As part of screening for participants who are eligible for the randomized trial, an ancillary study of prism adaptation testing will evaluate the initial response to relieving prism in the amount which would be prescribed if the participant were randomized to the prism group. The objective is to define the proportion of participants who fully prism adapt after 30 minutes of wearing "trial" relieving prism, defined as no reduction in magnitude of deviation by PACT when measured in relieving prism at both distance and near compared with the original deviation measured without relieving prism.

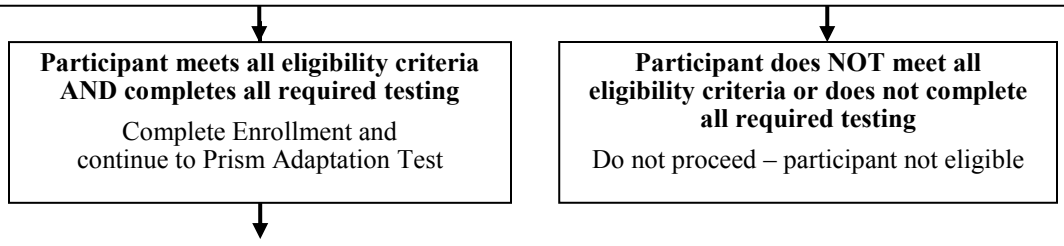
1.16 Study Flow Chart

Major Eligibility

- Ages 3 to < 13 years
- IXT (manifest deviation) meeting all of the following criteria:
  - IXT or constant XT at distance (mean distance control score of 2.0 or more) and with at least 1 measure of 3, 4 or 5)
  - IXT or exophoria at near (no control score of 5 on all 3 near assessments)
  - Distance deviation between 16Δ and 35Δ by PACT
  - Near deviation between 10Δ and 35Δ by PACT
  - Near deviation does not exceed distance by more than 10Δ by PACT
- No dissociated vertical deviation (DVD)
- No vertical >3Δ in primary gaze at distance, or near
- No pattern (such as "A" or "V") with a downgaze measurement of >10Δ difference from straight ahead (by PACT using investigator's routine method)
- No previous non-surgical treatment for IXT within the past 4 weeks (other than refractive correction), including vision therapy, patching, atropine, or substantial overminus spectacles, defined as spectacles overminused by more than 1.00D SE than the cycloplegic refractive error and ALSO results in minus SE power in the spectacles (i.e. underplussing is allowed)
- No prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- No prior use of prism spectacles
- Cycloplegic refraction within 7 months of enrollment (but prior to the day of enrollment)
- Refractive error between -6.00D SE and +2.50D SE (inclusive) (based on a cycloplegic refraction performed within 7 months, but prior to the day of enrollment)
- Distance visual acuity (any optotype) in both eyes according to age normal values as follows:
  - 20/50 or better for 3- to <4-year olds
  - 20/40 or better for 4- to <5-year olds
  - 20/32 or better for 5- to <7-year olds
  - 20/25 or better for ≥7-year olds
- Interocular difference of distance visual acuity ≤2 lines
- Must be wearing refractive correction (pre-study spectacles) for at least 1 week if refractive error (based on cycloplegic refraction performed within 7 months) meets any of the following:
  - SE anisometropia ≥1.00D
  - Astigmatism ≥1.00D in either eye
  - SE myopia ≥-0.50D in either eye
- If spectacles are worn, they must meet the following pre-enrollment criteria:
  - SE anisometropia corrected within 1.00D of full SE anisometropic difference
  - Astigmatism corrected within 1.00D of full magnitude; axis within 10 degrees if ≤1.00D and within 5 degrees if >1.00D
  - No overminus (i.e., no more than 1.00D more minus SE than full SE *if also* resultant minus SE)
  - No overplus (i.e., no more than 1.00D more plus SE than the full SE)

Enrollment Exam Testing Procedures

- Lensometry
- Symptom survey and spectacle surveys
- IXT control assessment #1(distance and near)
- Randot Preschool stereoacuity at near
- IXT control assessment #2 (distance and near)
- Cover Test (distance and near)
- Prism and Alternate Cover Test (distance and near, distance with -2.00D lens for AC/A)
- IXT control assessment #3 (distance and near)
- Fusional convergence amplitude testing (distance)
- Suppression assessment
- Distance visual acuity (any optotype)



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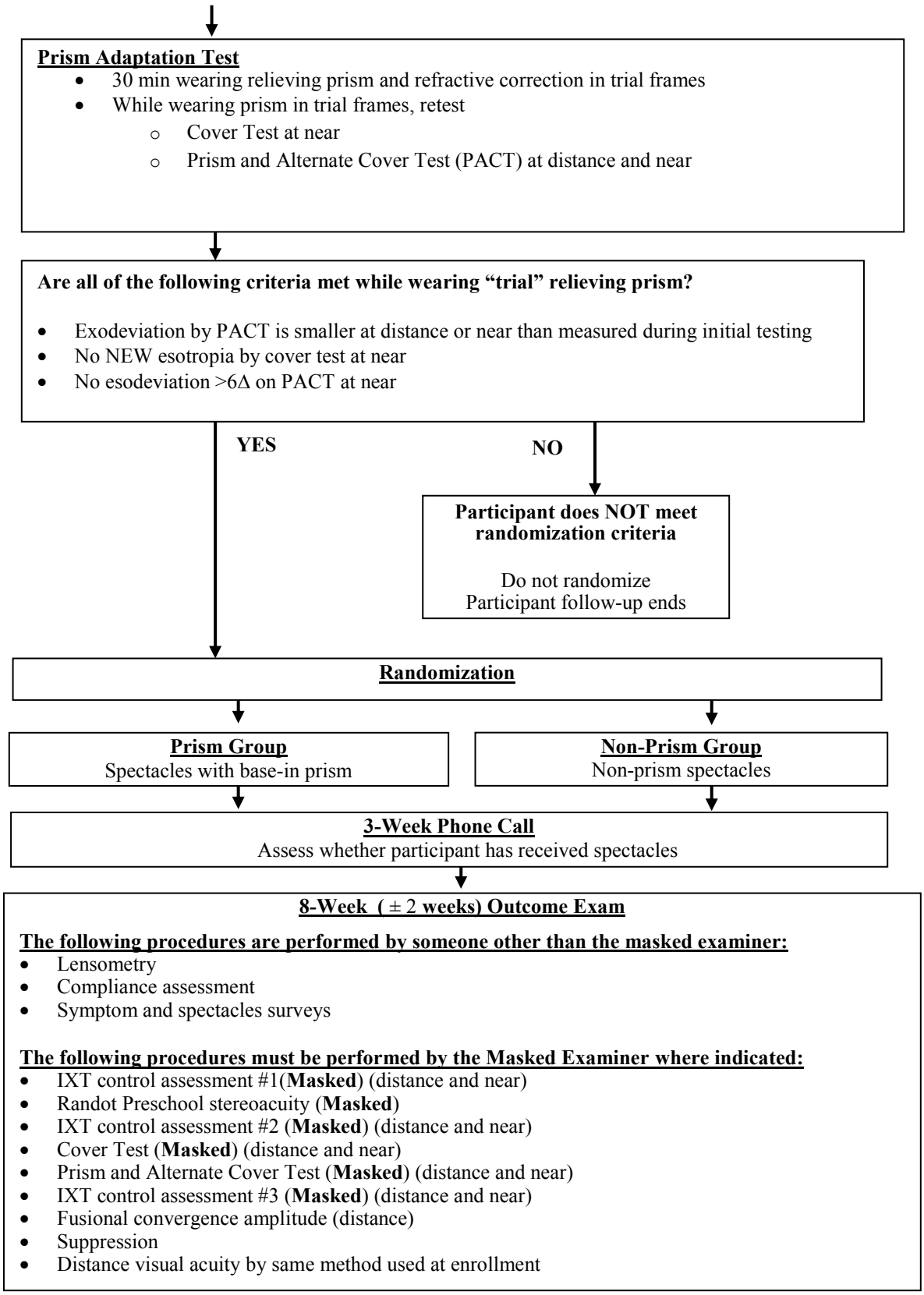
Prism Adaptation Test
30 min wearing relieving prism and refractive correction in trial frames
While wearing prism in trial frames, retest
Cover Test at near
Prism and Alternate Cover Test (PACT) at distance and near
Are all of the following criteria met while wearing "trial" relieving prism?
Exodeviation by PACT is smaller at distance or near than measured during initial testing
No NEW esotropia by cover test at near
No esodeviation >6Δ on PACT at near
YES
NO
Participant does NOT meet randomization criteria
Do not randomize
Participant follow-up ends
Randomization
Prism Group
Spectacles with base-in prism
Non-Prism Group
Non-prism spectacles
3-Week Phone Call
Assess whether participant has received spectacles
8-Week (± 2 weeks) Outcome Exam
The following procedures are performed by someone other than the masked examiner:
Lensometry
Compliance assessment
Symptom and spectacles surveys
The following procedures must be performed by the Masked Examiner where indicated:
IXT control assessment #1(Masked) (distance and near)
Randot Preschool stereoacuity (Masked)
IXT control assessment #2 (Masked) (distance and near)
Cover Test (Masked) (distance and near)
Prism and Alternate Cover Test (Masked) (distance and near)
IXT control assessment #3 (Masked) (distance and near)
Fusional convergence amplitude (distance)
Suppression
Distance visual acuity by same method used at enrollment

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CHAPTER 2 ENROLLMENT AND RANDOMIZATION

2.1 Eligibility Assessment and Informed Consent/Assent

A child is considered for the study after undergoing a routine eye examination (by a study investigator as part of standard care) where an IXT is identified and the child appears to meet the eligibility criteria for enrollment. 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 must be obtained from the parent prior to performing any study-specific procedures that are not part of routine care.

Participants aged 3 to <13 years with IXT who meet all eligibility criteria will be enrolled in the study and will undergo same-day prism adaptation testing. Depending on the results of the prism adaptation test, participants will either enter the randomized trial or will end study participation. Up to 100 participants will be enrolled in the study until at least 64 have been randomized. As the randomization goal approaches, sites will be notified of the end date for enrollment. Participants whose parents have signed an informed consent form can be enrolled and potentially randomized up until the end date, which means the randomization goal might be exceeded. The maximum number of participants who will be randomized is 80.

2.2 Eligibility Criteria for Enrollment

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

Inclusion Criteria

- Age 3 to < 13 years
- Intermittent exotropia meeting all of the following criteria:
  - Intermittent exotropia or constant exotropia at distance
    - Mean distance control score of ≥2.0 points (mean of 3 assessments over the exam) and with at least one measure of 3, 4, or 5, (spontaneous tropia) during control testing
  - Intermittent exotropia or exophoria at near
    - Child cannot have a score of 5 points on all 3 near assessments of control
  - Distance exodeviation at least 16Δ measured by PACT and no larger than 35Δ
  - Near exodeviation at least 10Δ measured by PACT and no larger than 35Δ
  - Near deviation does not exceed the distance deviation by more than 10Δ by PACT (convergence insufficiency-type IXT excluded)
- Distance visual acuity (by any optotype method) in both eyes according to age normal values[27, 28] as follows:
  - 20/50 or better for 3- to <4-year olds
  - 20/40 or better for 4- to <5-year olds
  - 20/32 or better for 5- to <7-year olds
  - 20/25 or better for ≥7-year olds
- Interocular difference of distance visual acuity ≤ 2 lines (0.2 logMAR)
- Refractive error between -6.00D SE and +2.50D SE (inclusive) (*based on a cycloplegic refraction performed within 7 months but prior to the day of enrollment*)
- Refractive correction (pre-study spectacles) worn for at least 1 week if refractive error (*based on cycloplegic refraction performed within 7 months*) meets any of the following:
  - SE anisometropia ≥1.00D

    - Astigmatism ≥1.00D in either eye
    - SE myopia ≥-0.50D in either eye
- If spectacles are worn, they must meet the following pre-enrollment criteria:
    - SE anisometropia corrected within <1.00D of full SE anisometropic difference
    - Astigmatism corrected within <1.00D of full magnitude; axis within 10 degrees if ≤1.00D of astigmatism and within 5 degrees if >1.00D of astigmatism
- Gestational age ≥ 32 weeks
- Birth weight >1500 grams
- Parent understands the protocol and is willing to accept randomization to prism spectacles or non-prism spectacles
- Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff and Investigator's site staff
- Relocation outside of area of an active PEDIG site within next 8 weeks is not anticipated

Exclusion Criteria

- Dissociated vertical deviation (DVD)
- Vertical deviation >3Δ in primary gaze at distance or near
- Pattern (such as an "A" or "V" pattern) with a downgaze measurement of >10Δ difference from straight ahead by PACT, measured by investigator's routine method
- Treatment for IXT or amblyopia (other than refractive correction) within the past 4 weeks, including vision therapy, orthoptics, patching, atropine, or other penalization
- Substantial overminus spectacles (spectacles overminused by more than 1.00D SE than the most recent cycloplegic refraction and ALSO results in minus SE power in the spectacles; i.e. underplussing is allowed) within the past 4 weeks
- Prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- Prior use of prism spectacles
- Current contact lens wear
- Abnormality of the cornea, lens, or central retina
- Down syndrome or cerebral palsy
- Developmental delay which would, in the opinion of the investigator, interfere with treatment or evaluation. Mild speech delays, reading disability, and learning disabilities are not excluded.
- Any condition that would, in the investigator's opinion, result in poor spectacle compliance
- Disease known to affect accommodation, vergence, or ocular motility such as multiple sclerosis, Graves orbitopathy, myasthenia gravis, diabetes mellitus, or Parkinson disease
- Current use of any ocular or systemic medication known to affect accommodation or vergence, such as anti-anxiety agents (e.g., Librium or Valium), anti-arrhythmic agents (e.g., Cifenline, Cibenzoline), anti-cholinergics (e.g., motion sickness patch (scopolamine)), bladder spasmolytic drugs (e.g., Propiverine), hydroxychloroquine, chloroquine, phenothiazines (e.g., Compazine, Mellaril, Thorazine), tricyclic antidepressants (e.g., Elavil, Nortriptyline, Tofranil)

Additional Eligibility Criteria for Randomization Based on Prism Adaptation Testing

- Exodeviation by PACT while wearing "trial" relieving prism is smaller at distance or near than measured during intial PACT testing (e.g. not fully adapting to prism at both distances)
- No NEW esotropia by cover test at near while wearing "trial" relieving prism
    - An esotropia at near also present on enrollment measurement is allowed because monofixational intermittent exotropia may be associated with a small angle esotropia
- No esodeviation >6Δ on PACT at near while wearing relieving prism

2.3 Historical Information

Historical information elicited will include the following: date of birth, sex, race, ethnicity, cycloplegic refraction, prior treatment for IXT, spectacle correction, and medical history.

2.4 Testing at the Enrollment Exam

All testing must be performed with the participant wearing "habitual correction" (with spectacles if child currently wears spectacles or without spectacles if child is not wearing spectacles).*

* The exception is for a participant who does not require spectacles per IXT6 protocol but is wearing a pair of spectacles that do not meet pre-enrollment spectacle tolerances (*see section 2.2*). This participant can have enrollment testing performed with or without these spectacles, provided the visual acuity eligibility criteria are met (*see section 2.2*). If visual acuity criteria are not met, the child is not eligible at that visit.

There is no specified "waiting" time that needs to occur between enrollment measurements, although testing must be performed without cycloplegia and in the following specified order at the enrollment visit:

1. Spectacle Prescription Verification (Lensometry):
    - Prior to performing the enrollment examination, the participant's habitual spectacle correction (if worn) is to be verified using a lensometer and compared with study spectacle requirements using procedures outlined in the IXT6 Testing Procedures Manual.
2. Symptom and Spectacle Surveys:
    - A brief survey of IXT symptoms will be administered to the child. Response options are based on frequency of observations: never, sometimes, and all the time.
    - A brief survey of symptoms that may be associated with prism spectacle wear such as headaches, eye strain, and problems with spectacle wear will be administered to the parent of the participant. Parents are asked to respond to the survey questions based on their observations of their child in the past 2 weeks. Response options are based on frequency of observations: never, rarely, sometimes, often, always, and not applicable.

STEPS 3 through 8 must be performed in the specified order by the same study-certified examiner (pediatric ophthalmologist, pediatric optometrist, or certified orthoptist) on the same day and without cycloplegia.

3. Control of the Exodeviation #1: Control of the exodeviation will be assessed in the habitual correction*(*see above*) in primary position at distance and near using the PEDIG IXT control scale (*see below*)[29] and as outlined the *IXT6 Testing Procedures Manual*.
   - Distance (6 meters) – fixing on an accommodative target such as a video or small letters
   - Near 1/3m (33cm)– fixing on Gulden near fixation target or similar accommodative target)
   - The scale below applies to both distance and near separately.

   Intermittent Exotropia Control Scale
   5 = Constant Exotropia
   4 = Exotropia > 50% of the 30-second period before dissociation
   3 = Exotropia < 50% of the 30-second period before dissociation
   2 = No exotropia unless dissociated, recovers in >5 seconds
   1 = No exotropia unless dissociated, recovers in 1-5 seconds
   0 = No exotropia unless dissociated, recovers in <1 second (phoria)
   Not applicable = No exodeviation present

Directions:

Step1: Assessment before any dissociation: Eye alignment is observed for a 30-second period with distance fixation. The time in seconds that a spontaneous IXT is observed is counted, and the appropriate control score (3, 4, or 5) is assigned for distance fixation. This is then repeated for near fixation for another 30-second period; if an exotropia is observed, then the time in seconds that an eye is observed to be exotropic is counted and the appropriate score of 3, 4, or 5 is assigned. If a score of ≥3 is present, then Step 2 (dissociation) is not required for that test distance. First distance and then near fixation are assessed before any dissociation (i.e., before step 2).

Step 2: Assessment with standardized dissociation is performed only if spontaneous exotropia is NOT observed during step 1 (control was not a 3, 4, or 5). Instead, control will be a 0, 1, or 2; this is determined based on the worst score determined from 3 successive 10-second periods of dissociation:
- An occluder is placed over the right eye for 10 seconds and then removed; the length of time it takes for the re-establishment of fusion is measured in seconds.
- The left eye is then occluded for a 10-second period (second assessment under dissociation) and after uncovering the eye, the time for re-establishment of fusion is similarly measured in seconds.
- A third assessment is performed, by covering the eye that required the longer time to re-fuse on the first two 10-second dissociations. After uncovering the eye, the length of time it takes for the re-establishement of fusion is measured in seconds.

The worst level of control for the three 10-second periods of dissociation by occlusion should be recorded.

Since the control score is the slowest time of the three assessments, if a score of 2 (>5 seconds recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

If the child has a micro-esotropia by the cover test but an exodeviation by PACT, the control scale applies to the exodeviation.

4. Stereoacuity Testing:
   - Stereoacuity will be assessed with habitual correction using the Randot Preschool stereotest at near (performed at 40 cm). A specific level of stereoacuity is not required for eligibility (i.e., a score of "nil" is allowed, but a child who, in the opinion of the investigator, does not understand the test would not be eligible.)
5. Control of the Exodeviation #2 (repeat) (see item #3):
   - The same examiner should assess IXT control for all three assessments of control during the enrollment visit.
6. Cover Test:
   - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
   - Cover Test will be assessed in primary position at distance (6 meters) and near (1/3 m), using procedures outlined in the IXT6 Testing Procedures Manual.
   - If the child has a micro-esotropia by the cover test but an exodeviation by PACT, the esodeviation will be recorded for the cover test.
7. PACT Testing & AC/A Determination:
   - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
   - PACT will be assessed in primary gaze using the IXT6-approved prism set and without cycloplegia at distance (6 meters) and near (1/3 m) in habitual correction. The procedure will include bracketing to find and record the high neutral endpoint as outlined in the *IXT6 Testing Procedures Manual*.
   - AC/A assessment is performed by measuring the PACT at distance (6 meters) with the participant wearing -2.00D lenses over the habitual correction. The AC/A ratio is calculated automatically by the website by taking the difference between the distance PACT measurements with and without the -2.00D lenses and dividing the difference by 2.
8. Control of the Exodeviation #3 (repeat) (see item #3):
   - The same examiner should assess control for all three assessments of control during the enrollment visit.
9. Fusional Convergence Amplitude Testing:
   - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist using procedures outlined in the IXT6 Testing Procedures Manual.
   - Fusional convergence amplitude to be measured at distance
   - Using the PEDIG-approved IXT6 prism bar, record the blur, break, and recovery points according to the IXT6 Testing Procedures Manual.
10. Suppression:
    - Assessment of suppression at distance using the Suppression Scale using procedures outlined in the IXT6 Testing Procedures Manual.
11. Distance Visual Acuity Testing:
    - Monocular distance visual acuity testing with the habitual correction and without cycloplegia will be measured using the investigator's usual method (recognition acuity using any optotype).
12. Additional Clinical Testing:
    - Ocular examination as per the investigator's clinical routine to rule out ocular abnormality or lens opacity (if not performed within 7 months)

2.5 Confirmation of Eligibility and Completion of Enrollment

Completion of enrollment will occur at the conclusion of the Enrollment Exam after confirming that all eligibility criteria are met. Participants not meeting all eligiblity criteria or who are unable to complete enrollment testing *other than fusional convergence amplitude and suppression testing* are not eligible for the study.

Eligibility criteria relating to refractive error and spectacle correction are based upon the cycloplegic refraction done within 7 months of enrollment.

- If all eligibility criteria are met the participant is enrolled and included in the Prism Adaptation Test Screening.
- If all eligibility criteria are not met, the participant is not enrolled or included in the Prism Adaptation Test Screening.

2.6 Prism Adaptation Test Screening

Participants who meet all enrollment criteria at the enrollment exam will undergo same-day prism adaptation testing. The results of the prism adaptation test will be used to determine eligibility for randomization.

2.6.1 Prism Adaptation Test

The prism adaptation test procedure is documented in the *IXT6 Testing Procedures Manual*.

- Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
- Testing must be done without cycloplegia.
- The purpose of testing is to assess a child's initial response to the amount of relieving prism that would be prescribed if randomly assigned to the prism spectacles group (*see table 1, section 3.1*).
- The examiner will place BOTH of the following in the IXT6 approved trial frame and have the child wear it continuously for at least 30 minutes:
  - Trial lenses equal to the amount of refractive correction in the habitual spectacles, or no correction if habitual lenses are not worn.
  - Trial prism lenses from the IXT6 trial prism set with protocol-determined amount of relieving prism (see table 1, section 3.1), with the following caveat:
    - To avoid the need for trial prisms of 3.5Δ for cases in which the total prism magnitude of 7Δ, a 4Δ prism will be placed in front of the eye that normally deviates, and 3Δ prism will be placed in front of the other eye.
- After 30 minutes of wearing the prism in trial frames, perform the following in primary position while the participant continues to wear the prism trial frames:
  - Cover test at near
  - PACT testing at distance and at near

2.7 Eligiblity for Randomization

The results of the prism adaptation test determine whether the participant is eligible for randomization or whether study participation will end.

Participants ARE eligible to be randomized if ALL of the following criteria are met:

- The participant has not fully adapted to prism at distance AND near

- The participant's PACT measurement at distance while wearing "trial" relieving prism is smaller than the originally measured deviation at distance OR near when not wearing prism (i.e., at least some reduction in deviation with prism)

- The participant has no NEW near esotropia by cover test while wearing the"trial" relieving prism (e.g., a microesotropia previously noted on near cover test during initial testing and also noted at this time is allowed)
- The participant has no esodeviation >6Δ on PACT at near while wearing "trial" relieving prism

Participants who fail to meet any of the above criteria will not be randomized and will discontinue study participation.

Examples:

Consider the following participants, each with a 30Δ exodeviation measured by PACT at both distance and near. These participants are now all wearing 40% relieving prism (12Δ, with 6Δ base-in in each lens) in a trial frame with habitual refractive correction. After 30 minutes of wearing prism, the participants have their deviation measured by the PACT in primary position **while wearing the trial frame including relieving prism**. Post- prism adaptation PACT measures are given in the following examples:

Patient is eligible based upon prism adaption and CAN be randomized.

1. Example 1 - No Prism Adaptation:
   Wearing prism, the participant now measures 18Δ exodeviation at distance by PACT and 18Δ exodeviation at near by PACT, and no esotropia by cover test at near. The angle has decreased by the amount of prism given, so there is no prism adaptation.
2. Example 2 - Partial Prism Adaptation:
   Wearing prism, the participant now measures 30Δ exodeviation at distance by PACT and 25Δ exodeviation at near by PACT, and no esotropia by cover test at near. The distance angle has not decreased while wearing prism but the near angle has decreased while wearing prism.
3. Example 3 – Pre-Existing Micro-Esotropia at Near:
   Wearing prism, the participant measures 18Δ exodeviation at distance by PACT and 18Δ exodeviation at near by PACT, but is esotropic at near by cover test (reflecting pre-existing monofixation; where, in this case, the tropia and phoria are in the opposite direction). The esotropia was present prior to prism adaptation.
   The PACT angle has decreased by the amount of prism given, so there is no prism adaptation.

Patient is NOT eligible based upon prism adaption and CANNOT be randomized.

1. Example 1 - Full Prism Adaptation:
   Wearing prism, the participant now measures 30Δ exodeviation by PACT at distance and near with the prism in place. The patient has completely adapted to the prism and is NOT eligible due to complete prism adaptation.

2. Example 2 – New Esotropia at Near:
   Wearing prism, the participant now measures 18Δ exodeviation at distance by PACT and 4Δ esodeviation at near by PACT and has an esotropia by cover test at near. The participant did not previously have an underlying esotropia. This participant is NOT eligible due to the new esotropia at near.
3. Example 3 – Esodeviation at Near now >6Δ by PACT:
   Wearing prism, the participant measures 18Δ exodeviation at distance by PACT and 8Δ esodeviation at near by PACT, although the participant is not esotropic at near by cover test. This participant is NOT eligible due to an esodeviation >6Δ at near by PACT while wearing prism.

2.8 Randomization

Randomization will occur within 7 days after the participant has met all eligibility criteria (Section 2.2), completes prism adaptation testing (Section 2.6), and meets the randomization criteria (Section 2.7).

Participants eligible for randomization will be randomly assigned with equal probability to one of the following groups:

- Prism group: spectacles with refractive correction (if required) and relieving prism as outlined in table 1 (*see section 3.1*)
- Non-prism group: spectacles with refractive correction (if required) and no prism

The Jaeb Center will construct a separate Master Randomization List using a permuted block design stratified by mean distance control score (2 to <3, 3 to <4, 4 to 5). A participant is officially randomized when the website randomization process is completed.

CHAPTER 3 TREATMENT AND FOLLOW-UP

3.1 Treatment for Prism Group

Participants assigned to the prism group will be prescribed spectacles with base-in prism ground into each lens. Total prism prescribed will be equal to 40% of the largest deviation at distance or near measured by PACT, with the total prism divided equally between the two lenses (Table 1). The prism spectacles must be worn all waking hours. No IXT treatment other than the prism spectacles can be prescribed for the duration of the study. Refractive correction will be prescribed according to criteria in section 3.3.

Table 1: Prescribed Prism According to Maximum Exodeviation

Maximum exodeviation by PACT (Larger Value of Distance or Near)	Total Base-in Prism Magnitude*	Base-in Prism Magnitude for Each Eye
16Δ	6Δ	3Δ
18Δ	7Δ	3.5Δ
20Δ	8Δ	4Δ
25Δ	10Δ	5Δ
30Δ	12Δ	6Δ
35Δ	14Δ	7Δ

*Total prism is 40% of the larger exodeviation comparing the distance and near PACT.

3.2 Treatment for Non-prism Group

Participants in the non-prism group will be prescribed non-prism spectacles according to refractive error correction criteria in section 3.3. No IXT treatment other than non-prism refractive correction can be prescribed for the duration of the study.

3.3 Post-Randomization Criteria for Refractive Error Correction

All participants in the study will be wearing spectacles following randomization and all those who habitually wore spectacles pre-study will be provided new spectacles for masking purposes (paid for by the study). All participants in both groups will be prescribed spectacles to correct their refractive error (or plano as appropriate) and those in the prism group will also have prism incorporated.

Refractive error correction for new spectacles for both groups will be calculated automatically by the study website and will meet all of the following criteria:

- Fully correct astigmatism (if present)
- If less hyperopic eye has SE myopia:
  - Prescribe the full sphere in both eyes
- If less hyperopic eye has SE hyperopia or emmetropia:
  - After correction of astigmatism, prescribe sphere so that spectacles will have plano SE in the less hyperopic eye
  - Match any reduction of sphere made to the less hyperopic eye in the fellow eye
- Prism (if in prism group) will be split equally between eyes (*see section 3.1*)

Participants in both groups must wear their refractive correction all waking hours.

NOTE: Because the study is providing spectacles to all randomized participants, those with any degree of refractive error (astigmatism, myopia, or anisometropia) will be prescribed spectacles with some refractive correction. Only participants who have no refractive error or have pure spherical hyperopia that is equal between both eyes will be prescribed plano lenses.

3.4 Follow-up Visit Schedule

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

- Telephone call: 3 weeks (21 to 28 days) after randomization to check that the spectacles have been dispensed/received and that the participant is wearing the new spectacles
- Outcome Visit: 8 weeks (±2 weeks) after randomization

Additional visits may be scheduled at investigator discretion although no data will be entered on the website.

3.5 Telephone Call

At 3 weeks following randomization, the site will contact the parents to determine whether the study-prescribed spectacles have been received and that the child is wearing them. The site will record the date that the new spectacles were received or document that they have not been received as of the call date. If spectacles have not been received, the site will record comments about factors involved in the delay. Sites will encourage full-time wear of the study spectacles.

3.6 Masked Examiner Testing

At the 8-week outcome visit, a Masked Examiner, who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist, will assess the control of the exodeviation and perform PACT testing (*see section 2.6.1*).

The Masked Examiner must be someone *other than* the investigator.

The Masked Examiner must not verify the spectacles using lensometry, discuss compliance of spectacle wear with the participant or parents, administer the symptom or spectacle survey, access the medical history, or enter data on the study website.

Given that the study spectacles will not be concealed in any way, instructions for the masked examiner will include the importance of maintaining masking if possible; examiners should try not to inspect the participants' spectacles during testing. After completion of the masked exam testing, the masked examiner will indicate whether or not the participant appears to be wearing prism correction.

3.7 Outcome Visit Testing Procedures

All outcome assessments should be completed with the participant wearing study spectacles (i.e., prism spectacles or non-prism spectacles).

Participants will be tested in trial frames in the following cases:

- Participant did not bring study spectacles to the outcome exam
- Participant's study spectacles are outside refractive error and/or prism tolerances
- Participant lost study spectacles
- Partcipant never received study spectacles

Someone *other than* the Masked Examiner will ensure that the participant is wearing the study-prescribed spectacles (including plano spectacles if prescribed) before the masked exam. The following procedures should be performed by the appropriate examiner (*see below*) and in the order specified:

The following procedures are tested first by someone *other than* the Masked Examiner:

1. Spectacle Prescription Verification (Lensometry): Prior to performing the outcome examination, the participant's spectacle correction will be verified using a lensometer (including plano lenses). *(See IXT6 Testing Procedures Manual)*
   - Lenses will be measured through the viewing position by marking the pupil position on the lenses and performing lensometry at this position
   - If spectacles do not meet the tolerances listed below, the participant should be tested with trial frames with the intended prescription in place.

Prism Group

- Spectacle sphere, cylinder, and axis should meet the following tolerances:
  - Sphere within 0.50D of prescribed
  - Astigmatism within 0.50D of prescribed
  - Axis within 10 degrees of prescribed astigmatism if ≤1.00D and within 5 degrees of prescribed astigmatism if >1.00D
- Spectacle prism should meet the following tolerances:
  - The **net** horizontal prism is <3Δ from the prescribed prism based on Table 1 (section 3.1)
  - The **net** vertical prism is <2Δ

Examples of Prism Spectacle Manufacture Tolerance

- Examples within tolerance:
  - 1Δ base-down both lenses (in addition to correct horizontal amount prescribed)
  - 3Δ base-in right lens, 5Δ base-in left lens when 4Δ base-in for both lenses was prescribed
- Examples NOT within tolerance:
  - 1Δ base-down right lens, 1Δ base-up left lens (in addition to correct horizontal amount prescribed)
  - 6Δ base-in right lens, 5Δ base-in left lens when 4Δ base-in for both lenses was prescribed

Non-Prism Group

- Spectacle sphere, cylinder, and axis should meet the following tolerances:
  - Sphere within 0.50D of prescribed
  - Astigmatism within 0.50D of prescribed
  - Axis within 10 degrees of prescribed astigmatism if ≤1.00D and within 5 degrees of prescribed astigmatism if >1.00D
- Because unintended prism can occur due to decentration, spectacle prism should meet the following tolerances:
  - The **net** horizontal prism is ≤1Δ
  - The **net** vertical prism is ≤1Δ

Examples of Non-Prism Spectacle Manufacture Tolerance

- Examples within tolerance:
  - 2Δ base down both lenses
  - 1Δ base in right lens, 1 base out left lens
  - No prism right lens, 1Δ base in left lens
- Examples NOT within tolerance:
  - 2Δ base-in right lens, 2Δ base-in left lens
  - 1Δ base up right lens, 1Δ base down left lens

2. Compliance Assessment: Compliance with spectacle wear since receiving the spectacles will be assessed based on review of the compliance calendars and discussion with the parents and child using the following scale:
   - Excellent (76% to 100%)
   - Good (51% to 75%)
   - Fair (26% to 50%)
   - Poor (≤ 25%)
3. Symptom and Spectacle Surveys:
   - A brief survey of IXT symptoms will be administered to the child.
   - A brief survey of symptoms that may be associated with prism spectacle wear will be administered to the parents of the participant. Parents are asked to respond to the survey questions based on their observations of their child in the past 2 weeks.

Once the assessments listed above are completed, the following procedures must be performed in the specified order. Procedures indicated as "masked" must be tested by the Masked Examiner. Procedures not indicated as "masked" may be tested by the Masked Examiner or another study-qualified examiner although it is preferred that they be completed by the Masked Examiner. All procedures should be performed with the participant wearing the study spectacles (or trial frames if required) and without cycloplegia:

Although testing must be performed in the specified order; there is **no specified** "waiting" time that needs to occur between different tests.

4. Control of the Exodeviation #1 **(Masked):** A Masked Examiner will assess control of exodeviation at distance and near fixation using the Intermittent Exotropia Control Scale.[29]
5. Stereoacuity Testing (**Masked**): Stereoacuity will be assessed using the Randot Preschool stereotest at 40 cm.
6. Control of the Exodeviation #2 **(Masked, *see item #4*)**
   - The same masked examiner who assessed IXT Control #1 does this second measure of control.
7. Cover Test **(Masked):**
   - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
   - Cover Test will be assessed in primary position at distance (6 meters) and near (1/3 m) using procedures outlined in the *IXT6 Testing Procedures Manual*.
8. PACT Testing **(Masked):** A Masked Examiner will assess the PACT in primary position

at distance (6 meters) and near (1/3 m) as outlined in the *IXT6 Testing Procedures Manual*.

9. Control of the Exodeviation #3 **(Masked, *see item #4)***
   - The same masked examiner who assessed IXT Control #1 & 2 does this third measure of control.
10. Fusional Convergence Amplitude Testing
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - Convergence amplitudes will be measured at distance
    - Using the PEDIG-approved IXT6 prism bar, record the blur, break, and recovery points according to the *IXT6 Testing Procedures Manual.*
11. Suppression:
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - Assessment of suppression at distance using the Suppression Scale and procedures outlined in the *IXT6 Testing Procedures Manual.*
12. Distance Visual Acuity Testing:
    - Monocular distance visual acuity testing without cycloplegia will be measured using the same method used at enrollment.

3.8 Additional Visits

Investigators may schedule additional visits at their discretion, although no data will be entered on the website.

3.9 Surgical or Non-Surgical Treatment

Strabismus surgery and non-surgical treatments for IXT, other than the study-prescribed spectacles, are not allowed during the study. If the investigator feels that additional treatment is needed outside of study guidelines, please contact a study chair for further clarification.

3.10 Treatment of Amblyopia

Given the exclusion of participants with amblyopia and the short duration of the trial, no treatment for amblyopia is allowed during the study.

3.11 Management of Refractive Error

Because of the short duration of the study, the spectacles prescribed at randomization may not be changed or discontinued without contacting a protocol chair.

In the event that spectacles are lost or damaged after randomization but before the outcome visit, the spectacles may only be replaced with the same spectacle prescription that was prescribed at randomization.

CHAPTER 4 MISCELLANEOUS CONSIDERATIONS 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 will contact the parents of the participants only when necessary. 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 participant and/or family and to help coordinate scheduling of the outcome examination.

The site investigator or coordinator will directly contact the parents of each participant 3 weeks after randomization to determine if the spectacles have been received, if the child is wearing the spectacles, and whether there are any concerns. Full-time wear of the spectacles will be encouraged.

4.2 Participant 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 the short duration of the study. 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.

4.3 Risks

There are no risks that would exceed standard of care treatment involved in this study when treating with either prism or non-prism spectacles.

4.3.1 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.

4.3.2 Risk of Prism Therapy

The risks involved in the study are identical to those for a child treated with prism therapy who is not participating in the study.

Some participants treated with prism may experience eye strain or notice distortion when wearing the spectacles; these typically dissipate over time and also with removal of the spectacles.

4.3.3 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.

4.4 Reporting Adverse Events

Although no adverse events are anticipated as a result of prism therapy or non-prism spectacle wear, any new cases of amblyopia or new cases of constant esotropia will be reported. No

surgical procedures are part of the protocol and no treatments are being prescribed that are not part of usual care. Investigators will abide by local IRB reporting requirements.

4.5 Discontinuation of Study

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

4.6 Travel Reimbursement

The parent of each participant enrolled in the study (i.e., undergoing prism adaptation testing) will be compensated $50 (by gift card or check) for completing the Enrollment Exam, regardless of whether the participant is randomized. The parent of each randomized participant will also receive an additional $50 (by gift card or check) for completing the 8-week outcome visit. If there are extenuating circumstances, and the participant is unable to complete the 8-week outcome visit without additional funds due to travel costs, additional funds may be provided.

4.7 Study Costs

The study will pay for visits that are done just for the research study. The participant or their insurance company will not be responsible for the cost of visits done just for the research study. The study will not pay for usual care visits. Usual care visits are those that would occur whether or not the subject is in the study. The cost of usual care visits will the responsibility of the participant or their insurance company.

- The study will pay for the 8-week study visit, as it is done just for the research study. Neither the participant or their insurance company will be responsible for the cost of the 8-week study visit.
- The study will pay for the participant's study glasses.

The study will not pay for contact lenses, tinted lenses, or antireflective coating.

4.8 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice.

Data will be directly collected in electronic CRFs, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

A risk-based monitoring approach will be followed, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013).

CHAPTER 5 SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The sample size and statistical analyses are summarized below.

The data collected in this short-term, pilot randomized trial will primarily be used to obtain preliminary estimates of treatment effect in both the prism and non-prism group to determine whether to proceed to a full-scale, longer-term randomized trial of prism vs. non-prism.

5.1 Sample Size

Because this study is a pilot study, sample size has not been statistically calculated. The sample size of 64 participants (32 participants per group) who pass the prism adaptation test (i.e., do not fully prism adapt) is a convenience sample that is expected to provide at least 60 participants (30 participants per group) for analysis after adjusting for up to 5% loss to follow-up.

The primary analysis section (section 5.2) indicates the level of statistical power/precision that the sample size of 30 participants per group (60 total) provides.

5.2 Primary Analysis

The primary analysis will be an intent-to-treat comparison of mean 8-week control of the distance exodeviation (average of 3 measurements) between treatment groups using an analysis of covariance (ANCOVA) model, which adjusts for baseline distance control.

5.2.1 Decision Guideline for Determining Whether to Proceed to a Randomized Trial

The data collected in this short-term, pilot randomized trial will primarily be used to determine whether to proceed to a full-scale, longer-term randomized trial of prism vs. non-prism. A decision guideline has been developed to aid in this decision (see below). The side effect profiles in each treatment group will also be considered when deciding whether to proceed with a full-scale trial.

The decision guideline for determining whether to proceed to a full-scale randomized trial will be based on the primary analysis estimate of the treatment group difference in mean distance control scores at 8 weeks. The standard deviation of 8-week distance control in IXT3 was 1.5 points (95% CI = 1.2 to 1.8 points). The convenience sample of 64 participants yields relatively low statistical power (61%) for detecting a difference if the true difference = -0.75 assuming an SD in the current study of 1.5 points and accounting for up to 5% loss to follow up. As the statistical power is poor, the decision guideline was based solely on the size of the observed difference in mean control scores (prism – non-prism). The decision is:

- **Proceed** if the observed difference ≤ -0.75 points
- **Uncertain** if the observed difference favors the prism group by less than 0.75 points (diff <0 and >-0.75)
- **Do not proceed** if the observed difference is zero or favors the non-prism group (diff ≥0)

*Note that differences (prism – non-prism) favoring prism will be negative given that lower control scores indicate better control.

Table 1: Probabilities of Proceed, Uncertain, and Do Not Proceed Decisions Given the True Treatment Group Difference in Means*

Decision Guideline #1: Whether to Proceed to Full-Scale Randomized Trial Based on OBSERVED Difference in Means in Pilot Study	TRUE Treatment Group Difference (Prism – Non-prism) (in points)				
	-0.25	**-0.50**	**-0.75**	**-1.0**	**-1.25**
Proceed** if observed difference is ≤-≤0.75	11%	27%	50%	73%	89%
Uncertain if observed difference is <0 and > -0.75	62%	62%	46%	26%	11%
Do not proceed if observed difference is ≥0	27%	11%	4%	1%	0%

* Table cells show the probability of making the given decision if the true difference is the given amount. Estimates were calculated using a 1-sided t-test, a standard deviation of 1.5 and 30 participants per treatment group.

** The 'proceed' row is the chance of observing a difference of 0.75 points or larger favoring prism given varying assumptions for the true treatment difference.

As seen in Table 1, the probability of making a 'proceed' decision when the true mean difference is -0.75 points or larger is 50%, the probability of an 'uncertain' decision is 46% , and the probability of a 'do not proceed' decision is 4%. Even if the true mean difference is as small as -0.50 points, the probablility of a "do not proceed" decision is still low at 11%.

5.3 Secondary Analysis -- Distance Control

The secondary analysis will calculate the proportion (and two-sided 95% confidence interval) of participants with a "treatment response," defined as ≥1 point improvement in control of their distance exodeviation (average of 3 measurements) between baseline and the 8-week outcome exam.

5.4 Secondary Analysis – No Spontaneous Tropia

The proportion of participants with no spontaneous tropia at 8 weeks will be compared between treatment groups using a two-sided Barnard's test with alpha of 0.05, with calculation of a two-sided 95% confidence interval on the difference in proportions.

No spontaneous tropia at the 8-week primary outcome exam is defined as a score of ≤2 (0, 1, or 2) on all three assessments of control at distance and at near.

5.5 Additional Analyses

5.5.1 Change in Distance Control

In addition to the primary analysis comparing mean change in distance control between treatment groups *(see section 5.2),* the distribution of change in distance control will also be compared between treatment groups using the Wilcoxon rank sum test.

5.5.2 Near Control

Near control will be evaluated similarly to the distance control in the primary analysis (*section 5.2*), secondary analyses (*section 5.3, 5.4),* and one of the additional analyses (*section 5.5.1*).

5.5.3 Ocular Alignment

The distribution of measures of ocular alignment at distance and near fixation by PACT will be described for the enrollment exam and the outcome exam for each treatment group. Because participants in the prism group will have PACT measured at 8-weeks while wearing study-prescribed relieving prism, we will account for this in analysis by adding the magnitude of the prescribed prism to the deviation by PACT while wearing prism for analysis of the total underlying deviation. We acknowledge this has limitations as measurement through ground in prism is not equivalent to measurement without ground in prism. The distribution of change in ocular alignment will also be described for each treatment group.

5.5.4 Near Stereoacuity

The distribution of near stereoacuity will be described for the enrollment exam and the outcome exam for each treatment group. The distribution of change in near stereoacuity will also be described for each treatment group.

5.5.5 Suppression

As an exploratory analysis, the distribution of suppression level (none, mild, moderate, severe) will be described for the enrollment exam and the outcome exam for each treatment group.

5.5.6 Fusional Convergence

As an exploratory analysis, the distribution of fusional convergence amplitude (break point, blur point, and recovery) will be described, and compared between treatment groups for the enrollment exam and the outcome exam for each treatment group.

5.5.7 Adverse Symptoms of Intermittent Exotropia and Prism Spectacle Wear

Adverse symptoms of IXT will be assessed at enrollment and at the 8-week outcome exam using a symptom survey that is administered to the child (*see section 2.4*). Response options are based on frequency of observations: never, sometimes, and always.

Similarly, adverse symptoms that may be associated with prism spectacle wear will be assessed at enrollment and at the 8-week outcome exam using a spectacle survey that is administered to the parent. Response options are based on frequency of observations: never, rarely, sometimes, often, always, and not applicable.

For each survey separately, the distribution of scores on each survey item will be described for the enrollment exam and the outcome exam for each treatment group.

5.5.8 Distance Visual Acuity

Distance visual acuity will be assessed at enrollment and at the 8-week outcome exam. Any optotype method can be used for testing; however, the same method must be used at both the enrollment and 8-week outcome exam.

The distribution of distance visual acuity measures will be described for the enrollment exam and the outcome exam for each treatment group. The distribution of change in visual acuity will also be described for each treatment group.

5.5.9 Compliance of Spectacle Wear

Parents will be asked to complete a compliance calendar by recording the percentage of time their child has worn the study-prescribed spectacle correction each day. Proportion of time worn each day will be described as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), poor (1 to 25%), or none (0%). Based on review of the calendars and discussion with parents at the 8-week outcome exam, the investigator will record the total proportion of time worn as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), poor (1 to 25%), or none (0%: did not fill prescription or never picked up spectacles).

The distribution of compliance will be assessed for each treatment group at the outcome exam.

5.5.10 Alternative Approach to Primary Analysis

A planned secondary analysis will be to repeat the primary analysis (*see section 5.2*) but limit it to participants who received their study spectacles in sufficient time to allow for the opportunity to have worn the spectacles for at least 4 weeks.

5.5.11 Mean Distance Control in Subgroups

As an exploratory analysis, the mean distance control score in subgroups based on baseline distance control severity will be estimated. The hypothesis for a subgroup effect based on distance control severity (2 to <3, 3 to <4, 4 to 5) is that poorer control is associated with larger treatment effect as suggested in a pilot study of overminus spectacles,[23] another form of non-surgical IXT treatment. Although the greater magnitude of response with poorer baseline control may have been at least partly attributable to regression to the mean and having more room for improvement, the same magnitude of response was not seen in the observation group, suggesting that the larger treatment effect with poorer baseline control observed when treating with overminus spectacles could be real.[23]

These planned subgroup analyses will repeat the primary analysis, adding the baseline factor and the baseline factor by treatment interaction. It is acknowledged that these analyses have very low power and only very strong interactions will be able to be detected. Any observed subgroup effects will require confirmation in a full-scale trial to be considered true effects.

5.5.12 Masking Assessment

At the 8-week visit, the proportion of masked examiners who responded that the patient appears to be wearing prism glasses will be compared between treatment groups using a two-sided Barnard's test with alpha of 0.05, with calculation of a two-sided 95% confidence interval on the difference in proportions.

5.6 Sample Size and Analysis for Prism Adaptation Testing Screening Study

In addition to the randomized trial, a separate analysis will include participants undergoing prism adaptation testing as part of screening for the randomized trial. The participants to be included will have met all randomized trial eligibility criteria other than that relating to the outcome of the prism adaptation test.

No formal sample size has been calculated. The convenience sample size will range between 64 to 100 participants, depending on the number of participants screened with prism adaptation test in order to enroll 64 participants in the randomized trial.

The analysis will be to estimate the proportion (and 95% confidence interval) of prism adaptation test-screened participants who fully prism adapt, defined as PACT after wearing relieving prism for 30 minutes (measured through the prism) ≥ original PACT (measured without prism) at both distance and near. The prism adaptation tests from the initial enrollment visit will be included for analysis; repeat enrollment prism adaptation tests will be excluded.

CHAPTER 6 REFERENCES

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