INTERMITTENT EXOTROPIA STUDY 2 (IXT2)

A Randomized Clinical Trial of Observation versus Occlusion Therapy 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 funded through a cooperative agreement from the National Eye Institute. It is one of a series of randomized trials and observational studies that address management of intermittent exotropia in children.

1.1 Background

Intermittent exotropia (IXT) is the most common form of childhood-onset exotropia with an incidence of 32.1 per 100,000 in children under 19 years of age.[1] Intermittent exotropia is characterized by an exotropia that is not constant and is mainly present in the distance but may also be present at near. Many cases of IXT are treated using non-surgical interventions,[2] such as part-time occlusion, fusional vergence exercises, and over-minus lenses. The rationale for such interventions is that they may improve the ability to control the IXT and preserve stereoacuity, thereby potentially addressing both visual function and social concerns, and may delay or eliminate the need for surgical correction of IXT. Nevertheless, the natural history of IXT is unknown and in many cases it is not known whether withholding treatment may in fact allow for spontaneous resolution or improvement in IXT, making non-surgical or surgical intervention unnecessary. Moreover, although non-surgical treatments for IXT are commonly prescribed,[2] such treatments have not been subjected to rigorous study and their efficacy in improving visual function or social concerns remains unclear.

One aim of the present study is to better understand the natural history of IXT. Available reports on the natural history of IXT disagree on the progression of the disease. A 1966 study by von Noorden (cited in von Noorden and Campos[3]) found that over an average of 3.5 years of follow-up, 75% of 51 patients showed signs of IXT progression, 9% showed no change, and 16% improved without therapy. A 1968 retrospective study by Hiles et al[4] found that after a minimum of 6 years follow up with observation and nonsurgical treatment, 81% of 48 patients showed no change in angle of deviation. The results of more recent retrospective studies show some reporting that the majority of cases improve over time,[5] others reporting that most cases remain stable,[6] and still others reporting that most cases deteriorate.[7] It is therefore unclear what proportion of patients, if left untreated, is likely to deteriorate, improve, or remain stable over time. Natural history data acquired during this study will help determine not only what proportion of patients change over time, but whether there are associated prognostic indicators of deterioration or improvement. Such data will not only enable better identification of those patients with IXT likely to benefit from treatment and those for whom treatment is likely to be unnecessary, but will also improve the quality of medical advice to parents regarding the likely progression of the disease, thus alleviating anxiety.

The aim of most forms of non-surgical treatments for IXT is to improve the strength and/or quality of binocular single vision by either eliminating suppression, increasing awareness of diplopia, and/or increasing positive fusional amplitudes. Commonly used non-surgical treatment methods include: occlusion,[8] fusional vergence exercises (sometimes known as vision therapy or orthoptics),[9] and over-minus lenses.[10] When surveyed in 1990, members of the American Association for Pediatric Ophthalmology and Strabismus reported that occlusion was the most commonly used form of non-surgical treatment.[11] More recently (2008), a poll of our investigator group revealed again that occlusion was the most widely prescribed non-surgical treatment for children affected by IXT.

Occlusion is thought to work by interrupting the development of or eliminating already present suppression, an adaptation to avoid diplopia in IXT. Persistent or entrenched suppression prevents normal binocular vision and may lead to permanent loss of stereoacuity.[12] If successful, occlusion may then result in improved binocular sensory fusion.

As reported in recent reviews of treatment for IXT,[2, 13] previous studies of occlusion vary regarding the recommended occlusion dose (from 3 hours a day to full time), the optimum duration of occlusion treatment (from 6 weeks to 42 months), and which eye should be occluded (preferred/dominant eye or alternate eyes).[2, 13] For the majority of studies, part-time occlusion, rather than full-time occlusion was preferred. In the three occlusion studies conducted prospectively, the recommended dose was either 3 hours a day,[14] 3 to 6 hours a day,[15] or 4 to 6 hours a day,[8] and the duration of occlusion ranged from 3 months[14] to 6 months[8] to up to 42 (mean 15) months.[15] Nevertheless, these previous studies of occlusion for the treatment of IXT used a variety of outcome measures at a variety of non-standardized time points; therefore, no definite conclusions can be drawn from the existing literature.

Although occlusion treatment for IXT treatment is widely used, there have been no randomized clinical trials evaluating its effectiveness. Understanding the degree of effectiveness of occlusion treatment for IXT and the natural history of IXT has important public health implications. Successful restoration of binocular alignment and normal binocular function with occlusion therapy, or spontaneous improvement, will reduce the proportion of children undergoing surgery. Defining the rate of success with either occlusion or observation is therefore important in planning treatment for children with IXT. Alternatively, evidence of low treatment effectiveness with occlusion will help avoid unnecessary treatment.

The present study is being conducted to assess the natural history of IXT and to establish the effectiveness of occlusion in its treatment.

1.2 Study Objective

- To determine the effectiveness of occlusion for the treatment of IXT among patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest
- To determine the natural history of IXT among patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest

1.3 Synopsis of Study Design

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

- Age 12 months to < 11 years
- Intermittent exotropia (manifest deviation) meeting all of the following criteria:
    - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
    - Exodeviation at least 15PD at distance OR near measured by prism and alternate cover test (PACT)
    - Exodeviation at least 10PD at distance measured by PACT
- No previous surgical or non-surgical treatment for IXT (other than refractive correction)

- Visual acuity in the worse eye at least 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS) for children ≥ 3 years of age
- No interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS) for children ≥ 3 years of age
- No hyperopia greater than +3.50 D spherical equivalent in either eye
- No myopia greater than -6.00 D spherical equivalent in either eye
- No prior strabismus, intraocular, or refractive surgery
- No abnormality of the cornea, lens, or central retina
- Investigator willing to observe the IXT untreated for 3 years unless specific criteria for deterioration are met

Sample size

The study will enroll 336 patients aged 3 years to < 11 years with near stereoacuity of 400 arcsec or better by the Preschool Randot stereotest at enrollment. An additional 80 patients will be enrolled for secondary cohorts during recruitment of the primary cohort.

Treatment

Randomization (1:1) to the following groups:

- Observation
- Occlusion treatment 3 hours per day for at least 3 months

Visit Schedule (timed from randomization)

- Enrollment exam
- 3 months ± 2 weeks
- 6 months ± 1 month
- 12 months ± 2 months
- 18 months ± 2 months
- 24 months ± 2 months
- 30 months ± 2 months
- 3 years ± 2 months

At each follow-up visit, distance and near ocular alignment, distance and near stereoacuity (children 3 years and older), and control of IXT (control score) is measured by a masked examiner. Distance visual acuity (for children 3 years and older) and health-related quality of life also will be measured (need not be masked).

Primary Cohort

The primary cohort consists of patients aged 3 years to < 11 years with near stereoacuity of 400 arcsec or better by the Preschool Randot stereotest at enrollment.

Primary Analyses

The proportion of primary cohort patients who meet the criteria for deterioration at the 6-month outcome exam will be compared between treatment groups and a 95% confidence interval for the difference in the proportions will be calculated.

The proportion of primary cohort patients in the observation group who meet the criteria for deterioration at the 3-year exam will be calculated and a 95% confidence interval calculated.

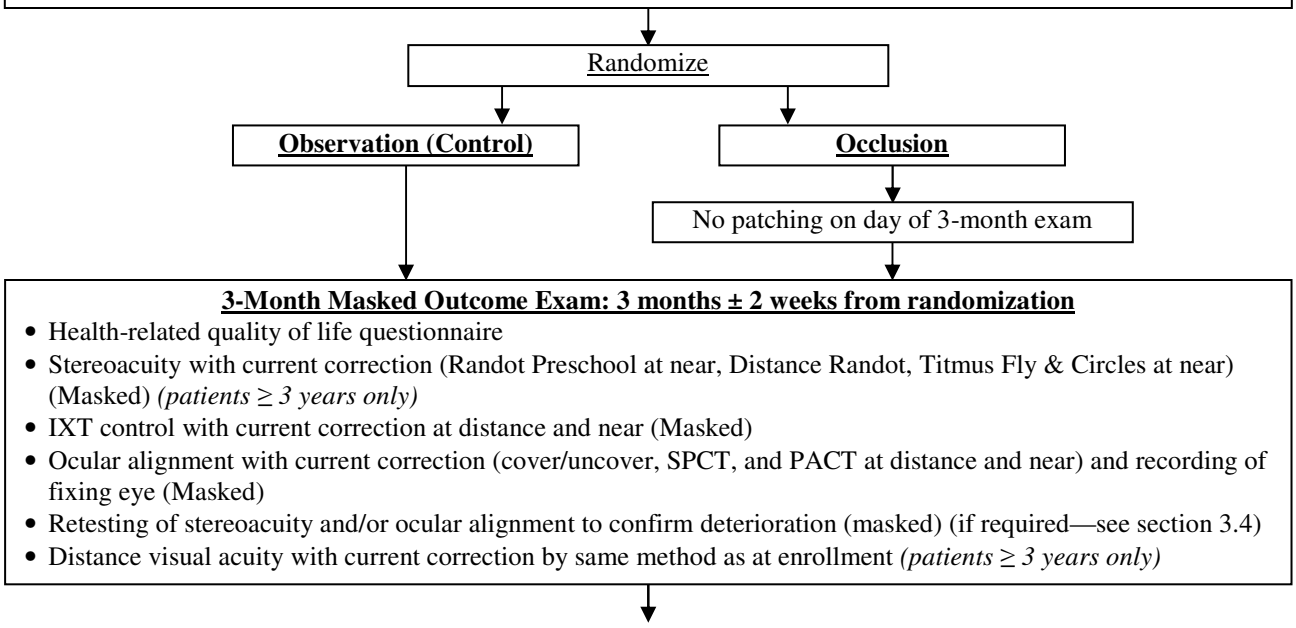
1.4 Study Flow Chart

Major Eligibility Criteria

- Age 12 months to < 11 years
- Intermittent exotropia (manifest deviation) meeting all of the following criteria:
  - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
  - Exodeviation at least 15PD at distance OR near measured by prism and alternate cover test (PACT)
  - Exodeviation at least 10PD at distance measured by PACT
- No previous surgical or non-surgical treatment for IXT (other than habitual refractive correction)
- Visual acuity in worse eye is at least 0.3 logMAR (20/40 by ATS HOTV for patients 3-<7 years or 70 letters E-ETDRS for patients >=7 years) *(patients ≥ 3 years only).*
- No interocular visual acuity difference of more than 0.2 logMAR (2 lines by ATS HOTV or 10 letters by E-ETDRS) *(patients ≥ 3 years only)*
- No hyperopia greater than +3.50 D spherical equivalent in either eye
- No myopia greater than -6.00 D spherical equivalent in either eye
- Wearing appropriate refractive correction for at least one week if refractive error meets refractive correction criteria
- No prior strabismus surgery, botulinum toxin injection, intraocular surgery, or refractive surgery
- No known skin reactions to patch or bandage adhesive
- No significant neurological impairment such as cerebral palsy
- No atropine use within the last week
- Gestational age > 34 weeks and birth weight > 1500 grams
- Investigator willing to observe the IXT untreated for 3 years unless specific criteria for deterioration are met

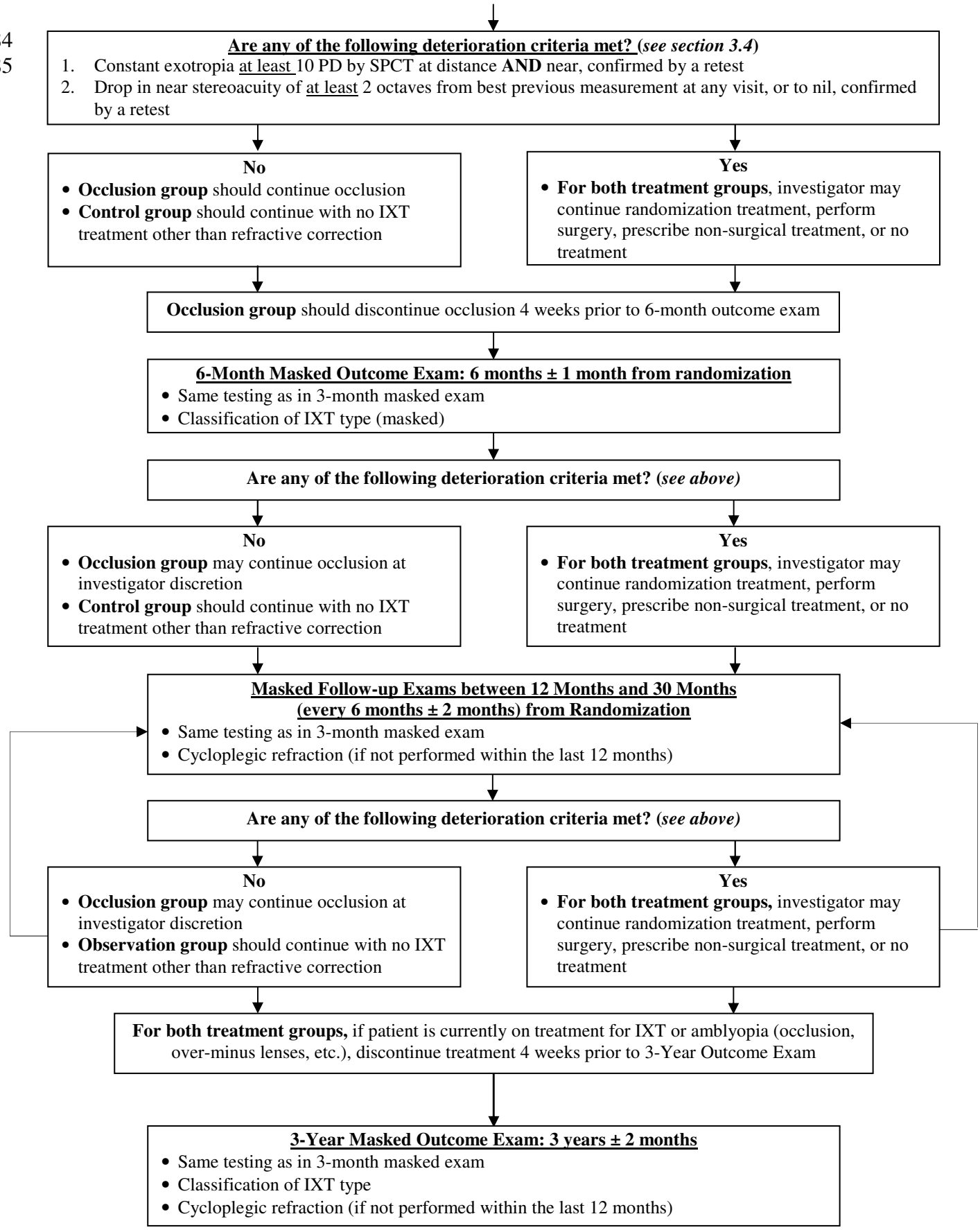
Enrollment Testing Procedures

- Health-related quality of life questionnaire
- Stereoacuity with current correction (Randot Preschool at near, Distance Randot, Titmus Fly & Circles at near) *(patients ≥ 3 years only)*
- IXT control with current correction at distance and near
- Ocular alignment with current correction (cover/uncover, SPCT, and PACT at distance and near)
- Classification of IXT type
- Distance visual acuity with current correction *(patients ≥ 3 years only)*
  - ATS HOTV for patients 3 to < 7 years or E-ETDRS for patients ≥ 7 years
- Ocular exam (if not done in last 6 months)
- Cycloplegic refraction (if not done in last 6 months)



3-Month Masked Outcome Exam: 3 months ± 2 weeks from randomization

- Health-related quality of life questionnaire
- Stereoacuity with current correction (Randot Preschool at near, Distance Randot, Titmus Fly & Circles at near) (Masked) *(patients ≥ 3 years only)*
- IXT control with current correction at distance and near (Masked)
- Ocular alignment with current correction (cover/uncover, SPCT, and PACT at distance and near) and recording of fixing eye (Masked)
- Retesting of stereoacuity and/or ocular alignment to confirm deterioration (masked) (if required—see section 3.4)
- Distance visual acuity with current correction by same method as at enrollment *(patients ≥ 3 years only)*


Are any of the following deterioration criteria met? (see section 3.4)
1. Constant exotropia at least 10 PD by SPCT at distance AND near, confirmed by a retest
2. Drop in near stereoacuity of at least 2 octaves from best previous measurement at any visit, or to nil, confirmed by a retest
No
• Occlusion group should continue occlusion
• Control group should continue with no IXT treatment other than refractive correction
Yes
• For both treatment groups, investigator may continue randomization treatment, perform surgery, prescribe non-surgical treatment, or no treatment
Occlusion group should discontinue occlusion 4 weeks prior to 6-month outcome exam
6-Month Masked Outcome Exam: 6 months ± 1 month from randomization
• Same testing as in 3-month masked exam
• Classification of IXT type (masked)
Are any of the following deterioration criteria met? (see above)
No
• Occlusion group may continue occlusion at investigator discretion
• Control group should continue with no IXT treatment other than refractive correction
Yes
• For both treatment groups, investigator may continue randomization treatment, perform surgery, prescribe non-surgical treatment, or no treatment
Masked Follow-up Exams between 12 Months and 30 Months (every 6 months ± 2 months) from Randomization
• Same testing as in 3-month masked exam
• Cycloplegic refraction (if not performed within the last 12 months)
Are any of the following deterioration criteria met? (see above)
No
• Occlusion group may continue occlusion at investigator discretion
• Observation group should continue with no IXT treatment other than refractive correction
Yes
• For both treatment groups, investigator may continue randomization treatment, perform surgery, prescribe non-surgical treatment, or no treatment
For both treatment groups, if patient is currently on treatment for IXT or amblyopia (occlusion, over-minus lenses, etc.), discontinue treatment 4 weeks prior to 3-Year Outcome Exam
3-Year Masked Outcome Exam: 3 years ± 2 months
• Same testing as in 3-month masked exam
• Classification of IXT type
• Cycloplegic refraction (if not performed within the last 12 months)

CHAPTER 2: ENROLLMENT AND RANDOMIZATION

2.1 Eligibility Assessment and Informed Consent

A minimum of 336 subjects are expected to be enrolled for the primary cohort (patients aged 3 to < 11 years who at enrollment have near stereoacuity of 400 arcsec or better by the Preschool Randot stereotest), with a goal to enroll an appropriate representation of minorities. In addition, up to 40 patients are expected to be enrolled in each of two secondary cohorts (patients aged 12 months to < 3 years and patients ≥ 3 years who are unable to perform near stereoacuity testing at enrollment; patients ≥ 3 years who have 800 arcsec or nil stereoacuity at near by Preschool Randot stereotest at enrollment) during recruitment for the primary cohort. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 436.

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

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility Criteria

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

1. Age 12 months to < 11 years
2. Intermittent exotropia (manifest deviation) meeting all of the following criteria:
   - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
   - Exodeviation at least 15PD at distance OR near measured by prism and alternate cover test (PACT)
   - Exodeviation at least 10PD at distance measured by PACT
3. No previous surgical or non-surgical treatment for IXT (other than refractive correction)
4. Visual acuity in the worse eye ≤ 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS) *(patients ≥ 3 years only).* Testing by ATS HOTV for patients 3 to < 7 years old and by E-ETDRS for patients ≥ 7 years old.
5. No hyperopia greater than +3.50 D spherical equivalent in either eye
6. No myopia greater than -6.00 D spherical equivalent in either eye
7. Patients must be wearing refractive correction (spectacles or contact lenses) for at least one week if refractive error (based on cycloplegic refraction performed within 6 months) meets any of the following:
   - Myopia > -0.50 D spherical equivalent in either eye
   - Anisometropia > 1.00 D spherical equivalent
   - Astigmatism in either eye > 2.00 D if ≤ 5 years old and > 1.50 D if > 5 years old

   Refractive correction for patients meeting the above refractive error criteria must meet the following guidelines:

- Anisometropia spherical equivalent must be within 0.25D of the full anisometropic difference correction
- Astigmatism cylinder must be within 0.25D of full correction and axis must be within 5 degrees of full correction.
- For hyperopia and myopia, the spherical component can be reduced by investigator discretion provided the reduction is symmetrical and results in residual (i.e., uncorrected) spherical equivalent refractive error that does not exceed +3.50D spherical equivalent hyperopia or -0.50 D spherical equivalent myopia.
- Deliberate over-minus using refractive correction with more than 0.50 D of over-minus will not be allowed. However, not prescribing the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overminusing for this protocol and is therefore allowed. It should be noted on the data collection form whether the current hyperopic correction was deliberately manipulated to better control the IXT.

Note that the refractive correction guidelines and the requirement to wear refractive correction for at least one week apply not only to patients who require refractive correction under the above criteria but also to any other patient who is wearing refractive correction.

8. No atropine use within the last week
9. Gestational age > 34 weeks
10. Birth weight > 1500 grams
11. Investigator is willing to observe the IXT untreated for 3 years unless specific criteria for deterioration outlined in *section 3.4* are met. Investigator also is willing to forgo extraocular muscle surgery for the first 3 months in all cases, and from 3 months to 3 years unless specific deterioration criteria outlined in *section 3.4* are met.
12. Patient and/or parent understands protocol, is willing to accept randomization to either observation or occlusion, and is willing to accept that surgical or other non-surgical treatment (other than occlusion in the occlusion group) of IXT will not be offered by the investigator unless specific deterioration criteria outlined in *section 3.4* are met.
13. Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff
14. Relocation outside of area of an active PEDIG site within next 3 years not anticipated

2.2.2 Exclusion Criteria

1. Pure phoria at both distance and near
2. Prior non-surgical treatment for IXT other than refractive correction (e.g., vergence therapy, occlusion, vision therapy/orthoptics, or deliberate over-minus with spectacles more than 0.50D)
3. Previous amblyopia treatment other than refractive correction within 1 year
4. Vision therapy/orthoptics for any reason within the last year
5. Interocular visual acuity difference more than 0.2 logMAR (2 lines on ATS HOTV for patients 3 to < 7 years old or 10 letters on E-ETDRS for patients ≥ 7 years old) *(patients ≥ 3 years only)* and/or investigator plans to initiate amblyopia treatment at this time.
6. Limitation of ocular rotations due to restrictive or paretic strabismus
7. Craniofacial malformations affecting the orbits
8. Ocular disorders which would reduce visual acuity (except refractive error)

9. Prior strabismus surgery or botulinum injection, intraocular surgery, or refractive surgery
10. Strabismus surgery planned
11. Known skin reactions to patch or bandage adhesives
12. Significant neurological impairment such as cerebral palsy. Patients with mild speech delays or common reading and/or learning disabilities are not excluded.
13. Investigator planning to change refractive correction at this time (if the patient is otherwise eligible, the investigator should consider prescribing refractive correction and bringing the patient back at a later time for enrollment)

2.3 Historical Information

Historical information elicited will include the following: date of birth, gender, race, ethnicity, and spectacle correction.

2.4 Procedures at the Enrollment Visit

1. Health-Related Quality of Life Questionnaire: Health-related quality of life (HRQOL) will be assessed using the Intermittent Exotropia Questionnaire (IXTQ).[16] This questionnaire consists of 3 components:
    1. Child questionnaire (for children ages 5 years or older) – consists of 12 items which assess how the child feels about his/her eye condition.
        - The version for children aged 5 to < 8 years has a three-level response scale (not at all, sometimes, a lot) and is administered by clinical staff either verbally or using a matching card.
        - The version for children aged 8 years and older has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered. However, it may be administered verbally by clinical staff if the child cannot read the questionnaire by him- or herself.
        - If possible, children should be positioned such that they are unable to view their parents during testing and parents should be advised not to influence their child's responses.
        - Children 4 years and younger will not complete the child questionnaire.
    2. Parent proxy questionnaire – consists of 12 items which assess how the parent feels the child's eye condition affects the child.
        - The questionnaire has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered.
    3. Parental questionnaire – consists of 17 items which assess how the child's eye condition affects the parent.
        - The questionnaire has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered.
2. Stereoacuity testing (patients >=3 years old only): stereoacuity will be assessed with current correction using the following:
    - Randot Preschool stereotest at near: If stereoacuity is worse than 40 arcsec, it must be retested and the better of 2 measures will be used as the stereoacuity for enrollment.
    - Distance Randot stereotest (performed at 3 meters)
    - Titmus Fly & Circles stereotest at near (note: Animals are not tested)

Stereoacuity should be tested before any other clinical testing is performed. If stereoacuity is not tested first, the patient must take a 10-minute break following any dissociative testing (e.g., visual acuity or ocular alignment) prior to testing stereoacuity.

Stereoacuity need not be present for eligibility. If the patient is unable to perform any of the stereoacuity tests, or has no measurable stereo, these findings will be recorded.

3. Control of exodeviation: Control of exodeviation will be measured at distance and near using the Office Control Score.[17]
   - Distance (6 meters) – fixating on an accommodative target such as a video for younger children or reading optotype letters for older children
   - Near (1/3 meter) – fixating on Lang-near viewing stick or similar accommodative target)

   The scale below applies to both distance and near.

   Intermittent Exotropia Control Scale[17]

   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)

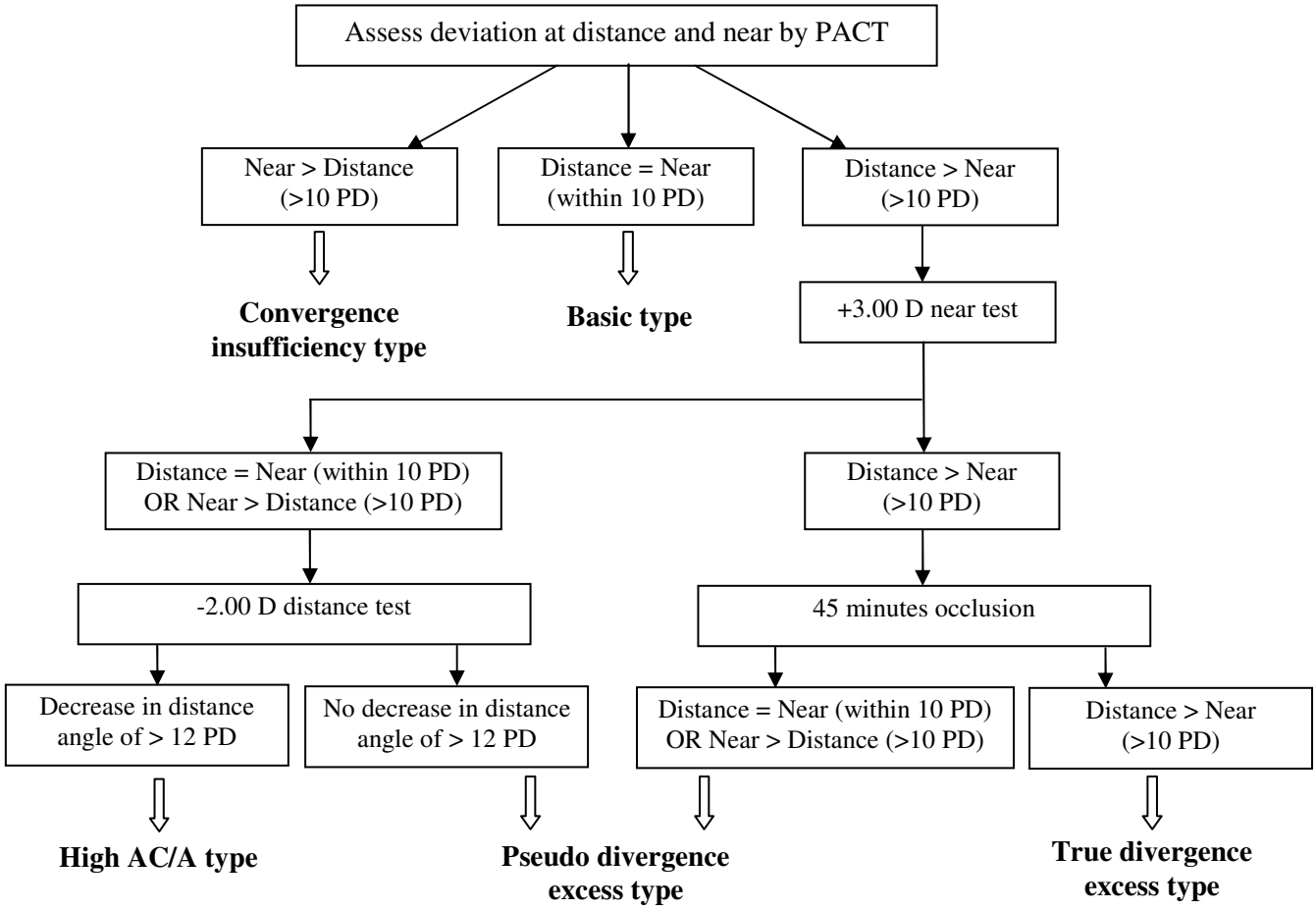
   - Levels 5 to 3 are assessed during a 30-second period of observation first at distance fixation and then assessed at near fixation for another 30-second period.
   - If no exotropia is observed during the 30-second period of observation, levels 2 to 0 are then graded as the worst of three rapidly successive trials:
     1. An occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to become re-established.
     2. The left eye is then occluded for a 10-second period and the time to re-establish fusion is similarly measured.
     3. A third trial of 10-second occlusion is performed, covering the eye that required the longest time to re-fuse.
   - The worst level of control observed following the three 10-second periods of occlusion should be recorded. If the patient has a micro-esotropia by SPCT but an exodeviation by PACT, the scale applies to the exodeviation.
   - Testing of control must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
   - Testing must be done prior to any dissociation or at least 10 minutes after any dissociation (including monocular visual acuity testing).
4. Ocular alignment testing:
   - Strabismic deviations will be assessed in current correction (either spectacles, contact lenses or trial frame) by the cover/uncover testing and then measured with the Simultaneous Prism and Cover Test (SPCT) (if tropia is of sufficient duration to measure) and Prism and Alternate Cover Test (PACT) in primary position at distance (6 meters) and near as outlined in the IXT Testing Procedures Manual
   - The deviation will be recorded as constant if a manifest tropia is present 100% of the time during the examination, determined by at least 3 cover/uncover tests (one must be before any dissociation), or as intermittent if a manifest tropia is present (including after dissociation) but not 100% of the time during the entire exam. The magnitude of the

deviation may change (vary) independently of the frequency of the deviation; frequency of tropia (constant vs. intermittent) is determined solely by whether the manifest tropia is present all or some of the time, including after dissociation. If a tropia is not observed at any time but a phoria is present, then the deviation will be recorded as not tropic (phoric only). If no deviation is present at any time, 'no deviation' will be recorded.
    - If the child appears to have a constant tropia but shows excellent stereoacuity that may be inconsistent with the diagnosis of constant tropia, the examiner should look over the child's polarized glasses to determine whether the child is indeed constantly tropic (by direct observation by cover/uncover test).
- The deviating eye will be recorded as "right", "left", or "alternates."
- Testing will be performed following control of exodeviation testing and prior to any cycloplegia.
- Ocular motility will be assessed including: ductions, oblique muscle overactions, dissociated vertical deviations, and nystagmus
- Ocular alignment testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

5. <u>Classification of IXT type:</u>

Classification of IXT type will be done as follows (*also see flowchart on next page*):
Using the PACT at distance and near:

- If the measured deviation at near is > 10 PD larger than at distance, the IXT is classified as **convergence insufficiency type**.
- If the distance and near deviations are within 10 PD of one another, the IXT is classified as **basic type**.
- If the measured deviation at distance is > 10 PD larger than at near, +3.00 D lenses should be placed over the current correction (using trial frames or Halberg clips) and the deviation at near should be re-measured by the PACT.
    - If the angles equalize (distance and near within 10 PD) OR near exceeds distance by > 10 PD, the +3.00 D lenses at near should be removed and -2.00 D lenses should be placed over the current correction (using trial frames or Halberg clips) and the deviation at distance should be re-measured.
        - If the distance angle with the -2.00 D lenses decreases by > 12 PD (compared to the distance measure without the -2.00 D lenses), the IXT type is classified as **high AC/A type**; otherwise the IXT type is classified as **pseudo divergence excess type**.
    - If the distance angle exceeds near by >10PD measured with the +3.00 D lenses at near, the patient should be occluded for 45 minutes, after which the distance and near deviations should be measured again in the current refractive correction, while maintaining the dissociation. If the near and distance deviations equalize (within 10 PD) or if near exceeds distance, the type of IXT is classified as **pseudo divergence excess type**. Otherwise, the type IXT is classified as **true divergence excess type**.



6. Visual Acuity Testing (patients >=3 years old only): Distance visual acuity testing will be performed with current correction and without cycloplegia, by a certified examiner with the Electronic Visual Acuity Tester (EVA) using the ATS single surround HOTV for patients 3 - < 7 years old and using the E-ETDRS for patients ≥ 7 years.
   - The protocol for conducting visual acuity testing is described in the ATS Testing Procedures Manual.
   - The same visual acuity testing method used at enrollment will be used throughout the study.
   - No acuity data (including fixation preference) will be collected on children < 3 years old.
7. Additional Clinical Testing:
   1. Ocular examination as per investigator's clinical routine (if not performed within 6 months)
   2. Cycloplegic refraction (if not performed within 6 months)
      - See *section 2.2.1* for eligibility criteria related to refractive error.

2.5 Randomization of Eligible Patients

Patients enrolled in the study will be randomized with equal probability to one of the following groups:

1. Observation
2. Occlusion 3 hours per day for at least 3 months

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

If assigned to the occlusion group, treatment must commence within 48 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 separate Master Randomization List using a permuted block design stratified by site and whether the patient is in the primary cohort, which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed.

CHAPTER 3: TREATMENT AND FOLLOW-UP

3.1 Treatment

3.1.1 Observation Group

Patients randomized to the observation group will receive no treatment (other than refractive correction).

If a patient meets deterioration criteria (*section 3.4*) at any visit 3 months or later, treatment for the remainder of the study is at investigator discretion--the investigator may continue to observe the patient, perform surgery, or initiate occlusion or other non-surgical treatment.

If a patient does not meet deterioration criteria, the patient will continue to receive no treatment for IXT other than spectacle correction.

3.1.2 Occlusion Group

Patients randomized to the occlusion treatment group will receive occlusion for 3 hours per day for at least 3 months. Choice of which eye to occlude, or whether to alternate daily, is at investigator's discretion and will be recorded.

At the 3-month visit:

- If a patient meets deterioration criteria (*section 3.4*), treatment for the remainder of the study is at investigator discretion – the investigator may continue occlusion, perform surgery, or initiate other non-surgical treatment.
- If a patient does not meet deterioration criteria, the patient will continue occlusion 3 hours per day until 4 weeks before the 6-month visit.

Patients who are being treated with occlusion should discontinue occlusion 4 weeks before the 6-month visit.

At any visit 6 months or later:

- If a patient meets deterioration criteria (*section 3.4*), treatment for the remainder of the study is at investigator discretion – the investigator may continue occlusion, perform surgery, initiate other non-surgical treatment, or prescribe no treatment.
- If a patient does not meet deterioration criteria, the patient will continue to receive either occlusion or no treatment for IXT other than refractive correction at investigator discretion.

3.2 Follow- up Visit Schedule

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

- 3-month: 3 months ± 2 weeks
- 6-month: 6 months ± 1 month
- 12 months ± 2 months
- 18 months ± 2 months
- 24 months ± 2 months
- 30 months ± 2 months
- 3-year: 3 years ± 2 months

At follow-up visits, distance and near ocular alignment, distance and near stereoacuity (children 3 years and older), control of IXT (control score), and classification of IXT (6 months and 3 year visits only) are performed by a masked examiner. Visual acuity and health-related quality of life are also assessed (need not be masked).

Additional non-specified visits may be scheduled at investigator discretion.

3.3 Follow-up Testing Procedures

Prior to the patient's examination, his/her spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., noncycloplegic retinoscopy) should be performed.

The following procedures should be performed in the order specified:

1. Health-Related Quality of Life Questionnaire: Health-related quality of life (HRQOL) will be assessed as described in *section 2.4* at all follow-up visits before any clinical testing.
2. Stereoacuity testing (masked) (*section 2.4 and 3.5*) (patients >=3 years old only): stereoacuity will be assessed with current correction using the following:
   - Randot Preschool stereotest (Near)
   - Distance Randot stereotest (Distance)
   - Titmus Fly & Circles stereotest (Near) (note: Animals are not tested)
   - In the case of a protocol testing order violation, stereoacuity should be performed 10 minutes after any dissociation.
3. Control of exodeviation (masked) (*section 2.4 and 3.5*): Control of the exodeviation will be measured at distance and near using the Office Control Score[17]
4. Ocular alignment testing (masked) (*section 2.4 and 3.5*):
   - Ocular alignment with current correction in the primary position using cover/uncover, SPCT (if tropia is of sufficient duration to measure), and PACT, both at distance and near fixations, in current correction without prism.
     - Testing must be performed without cycloplegia.
5. Classification of IXT type (6-month and 3-Year Outcome exams only) (masked): Classification of IXT type will be performed as described in *section 2.4.*
6. Retesting of stereoacuity and/or ocular alignment to confirm deterioration (masked) (if required)
   - If any of the deterioration criteria appear to be met (*section 3.4*) based on initial testing, the criterion met will be retested by a masked examiner (*section 3.5*).
   - All retesting should be performed at least 10 minutes after the initial ocular alignment testing.
7. Visual Acuity (patients >=3 years old only): Visual acuity testing at all follow-up exams will be done at distance with current correction and without cycloplegia by a certified examiner using either the ATS single-surround HOTV letter protocol or the E-ETDRS protocol on the Electronic Visual Acuity Tester. For each patient, visual acuity must be measured with the same visual acuity protocol used at enrollment.
8. Cycloplegic refraction (if not performed within the last 12 months)
   - Management of refractive error is subject to the guidelines in *section 4.3.*
   - For patients wearing contact lenses, an overrefraction should be performed to verify the correction.

3.4 Deterioration Criteria

A patient's condition will be considered to have deteriorated if any of the following criteria are met during masked examiner testing (*section 3.5*)* at any protocol-specified or additional visit occurring 3 months from randomization or later:

1. Constant exotropia at least 10 PD at distance **AND** near (throughout exam) by SPCT, confirmed by a retest
    - Constant is defined as an exotropia present throughout the examination and determined by at least three cover/uncover tests performed at various times during the exam (one must be before any dissociation).
2. Drop in near stereoacuity by Preschool Randot stereotest of at least 2 octaves (at least 0.6 log arcsec) from the best previous near stereoacuity measurement at any visit (including enrollment) (*see Table 1*), or to nil, confirmed by a retest
    - For children not able to perform near stereoacuity testing at enrollment, the near stereoacuity deterioration only apply after near stereoacuity measurements have been obtained at a follow-up visit.

Table 1: Preschool Randot Stereotest

Best stereoacuity at any previous visit (including enrollment), in arcsec	Level needed at follow up visit to meet deterioration criteria, in arcsec
40"	200" or worse
60"	400" or worse
100"	400" or worse
200"	800" or worse
400"	Nil
800"	Nil
Nil	Not applicable

*Note that both the initial testing and the retest must be performed by a masked examiner (*section 3.5*). All retesting should be performed at least 10 minutes after the initial ocular alignment testing.

If a patient appears to have met one or more of the above deterioration criteria but the retest(s) do not confirm that at least one criterion is met, the patient's condition is not considered to have deteriorated.

For analysis, patients will also be considered to have had their condition deteriorate if for any reason they undergo surgery or initiate any nonsurgical treatment for IXT (other than occlusion treatment in the occlusion group).

- Note that patients undergoing treatment for amblyopia are expected to be rare and such patients will not be classified as having had deterioration unless they meet criteria for deterioration, undergo surgery, or initiate non-surgical treatment for IXT (other than occlusion in the occlusion group).

3.5 Masked Examiner Testing

At follow-up visits, the IXT control assessment, ocular alignment, classification of IXT type (6 months and 3 year visits only), and stereoacuity testing must be performed (*section 2.4*) by a masked examiner.

All retesting should be performed at least 10 minutes after the initial ocular alignment testing.

- First, if the deterioration criterion related to a drop in near stereo appears to be met (*section 3.4*) by the masked exam testing, Preschool Randot stereotest at near must be retested by the masked examiner.
- Second, if the deterioration criterion related to a constant exotropia appears to be met (*section 3.4*) by the masked exam testing, cover/uncover testing and SPCT at distance and near must be retested by the masked examiner.

Because the masked examiner must be masked to the patient's treatment group, he/she must be someone other than the investigator.

3.6 3-Month Masked Exam

Both the observation and occlusion groups will return for a masked exam at 3 months ± 2 weeks following randomization. Patients in the occlusion group will continue to patch up to the day prior to the exam--patients must not patch on the day of the exam. Patients in the occlusion group must resume patching following the 3-month masked exam unless they have met deterioration criteria (*section 3.4*).

Prior to the patient's examination, his/her spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., noncycloplegic retinoscopy) should be performed.

At this exam, the following are tested in the specified order (*section 3.3*):

- Health-related quality of life
- Stereoacuity at distance and near with current correction (masked) (patients ≥ 3 years old only)
- Control at distance and near with current correction (masked)
- Ocular alignment at distance and near with current correction (masked)
- Distance visual acuity with current correction (patients ≥ 3 years old only)

For patients in the occlusion group, the examiner will record whether compliance with occlusion (according to the parents) appears to have been more than prescribed (>100% prescribed), excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), or poor (< 25%). The examiner will also record whether the patient patched on the day of the exam.

If deterioration criteria are met at this exam, investigators may treat the IXT at their discretion (*section 3.1*). The patients will continue to be seen at scheduled visits throughout the study.

If deterioration criteria are not met at this exam:

- Patients randomized to the occlusion group must continue occlusion 3 hours per day.
- Patients randomized to the observation group must continue with no IXT treatment other than refractive correction.

Schedule the 6-month visit at this time. Instruct the parents of patients in the occlusion group to discontinue patching 4 weeks prior to their scheduled 6-month masked outcome exam.

3.7 6-Month Masked Exam

The 6-month masked outcome exam will occur 6 months ± 1 month following randomization.

Patients in the occlusion group should have discontinued patching 4 weeks prior to this exam. These patients will receive a call from the Jaeb Center 4 weeks prior to the 6-month exam to remind them to discontinue patching. Failure to discontinue patching will be recorded at the 6-month exam. Compliance with occlusion will be recorded at this exam.

Prior to the patient's examination, his/her spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., noncycloplegic retinoscopy) should be performed.

At this exam the same procedures in the same sequential order will be conducted that were conducted at the 3-month exam (*section 3.6*). In addition, classification of IXT type will be performed (*sections 2.4 and 3.3*) by the masked examiner.

If deterioration criteria (*section 3.4*) are met at any exam 3 months or later, investigators may treat the IXT at their discretion (*section 3.1*). The patient will continue to be seen at scheduled visits throughout the study.

If deterioration criteria (*section 3.4*) are not met at any exam 3 months or later:

- Patients randomized to the occlusion group may resume occlusion (duration at investigator discretion) after the 6-month masked exam at the investigator's discretion.
- Patients randomized to the observation group should continue with no IXT treatment other than refractive correction.

3.8 Masked Exams Every 6 Months between 12 Months and 30 Months

All patients will continue follow-up at 6 months ± 2 month intervals. Prior to the patient's examination, his/her spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., noncycloplegic retinoscopy) should be performed.

At this exam the same procedures will be conducted that were conducted at the 3-month exam (*section 3.6*). In addition, cycloplegic refraction will be performed unless it was performed within the past 12 months (*sections 2.4 and 3.3*). For patients in the occlusion group, compliance with occlusion will be recorded if applicable.

If deterioration criteria (*section 3.4*) are met at any exam 3 months or later, investigators may treat the IXT at their discretion (*section 3.1*). The patients will continue to be seen at scheduled visits throughout the study.

If deterioration criteria (*section 3.4*) have not been met at any exam 3 months or later:

- Patients randomized to the occlusion group may be prescribed occlusion at the investigator's discretion.

- Patients randomized to the observation group should continue with no IXT treatment other than refractive correction.

3.9 3-Year Masked Exam

All patients will have a 3-Year Masked Outcome Exam at 3 years ± 2 months.

If a patient is currently on treatment for IXT or amblyopia (occlusion, over-minus lenses, etc.), treatment must be discontinued 4 weeks prior to 3-Year Outcome Exam. The parent will receive a call from the Jaeb Center 4 weeks prior to the 3-year exam to remind them to discontinue any current therapy. Failure to discontinue patching will be recorded at the 3-year exam.

Prior to the patient's examination, his/her spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., noncycloplegic retinoscopy) should be performed.

At this exam the same procedures will be conducted that were conducted at the 3-month exam (*section 3.6*). In addition, classification of IXT type will be made (*sections 2.4 and 3.3*) by the masked examiner.

A patient will be considered to have deteriorated if any of the deterioration criteria are met (*section 3.4*).

3.10 Additional Visits

Investigators may schedule additional visits at their own discretion. If the investigator feels the patient has met deterioration criteria, then he or she must arrange a masked examiner testing (*section 3.5*) to determine deterioration before initiating any alternative treatment. If the masked exam testing does not confirm that the deterioration criteria have been met, no treatment (other than occlusion in the occlusion group) can be started.

Patient will continue to follow the regular follow-up exam schedule following an additional visit.

3.11 Strabismus Surgery or Non-Surgical Treatment

While enrolled in the study, the investigator can only* perform strabismus surgery or initiate non-surgical treatment for IXT (other than occlusion in the occlusion group) (*section 3.1*) after one or more of the deterioration criteria are met (*section 3.4*).

*The following are exceptions under which an investigator may elect to perform strabismus surgery or initiate non-surgical treatment for IXT (other than occlusion in the occlusion group) in the absence of the patient meeting any of the deterioration criteria (*section 3.4*):

- Presence of debilitating diplopia
- Presence of overwhelming social concern (child or parent)
- Failure to keep up with stereoacuity age-norms (a patient with age-normal near stereoacuity at baseline or follow up fails to keep up with age norms during subsequent follow up (*see Table 2*), the subnormal stereoacuity is confirmed by a repeat test, and the investigator feels strongly that it is in the best interest of the patient to intervene)

Table 2: Age Norms for Near Stereoacuity by Preschool Randot Stereotest**

Age (in years)	Normal Range (arc sec)	Subnormal (arc sec)
3	40” to 400”	worse than 400”
4 to 5	40” to 200”	worse than 200”
6	40” to 100”	worse than 100”
7 to 17	40” to 60”	worse than 60”

**Based on data from Birch et al[18]

Note that for the above three exceptions, the patient’s condition will be considered a deterioration for analysis only if it leads to surgical or nonsurgical treatment (other than occlusion in the occlusion group).

3.12 Treatment of Amblyopia

Treatment of amblyopia is allowed at any point after the 6-month exam if a patient has an interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters by E-ETDRS) with a worse eye visual acuity of worse than 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS). If the investigator elects to prescribe patching for amblyopia, the eye with the better visual acuity will be patched. Patching for amblyopia treatment must be done for at least 2 hours per day for observation group patients and for at least 3 hours per day for the occlusion group patients. Treatment of amblyopia with atropine, overplus spectacle lenses, Bangerter filters, or vision therapy/orthoptics is not allowed. Any amblyopia treatment will be recorded at the next study visit.

All amblyopia treatment must be stopped for 4 weeks immediately prior to the 3-year outcome exam.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

4.1 Contacts by the Jaeb Center for Health Research

The Jaeb Center will maintain direct contact with the parents of each patient at least 2 times per year. 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 patient and/or family and to help coordinate scheduling of the outcome examinations. Additional contacts will be made if necessary for the scheduling of follow-up visits.

4.2 Patient 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. 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 patient in the study under the new provider's care.

4.3 Management of Refractive Error

A cycloplegic refraction should be performed every 12 months. In addition, a refraction should be performed whenever the investigator suspects that refractive error may not be optimally corrected.

For patients whose refractive error meets criteria for requiring a refractive correction (*section 4.3.1*), the correction prescribed should meet the refractive correction guidelines found in *section 4.3.2*.

For patients whose refractive error does not meet the criteria for a required correction (*section 4.3.1*), it is at investigator discretion whether to prescribe a correction; however, if refractive correction is prescribed, it should meet the refractive correction guidelines found in *section 4.3.2*.

4.3.1 Refractive Error Requiring Correction

The following are the criteria for requiring refractive error correction:

- Myopia > -0.50 D spherical equivalent in either eye
- Hyperopia > +3.50 D spherical equivalent in either eye
- Anisometropia > 1.00 D spherical equivalent
- Astigmatism in either eye > 2.00 D if ≤ 5 years old and > 1.50 D if > 5 years old

4.3.2 Refractive Correction Guidelines

The following are the guidelines for refractive correction which apply to patients meeting criteria for requiring refractive error correction *(section 4.3.1)* and any patients wearing refractive correction:

- Anisometropia spherical equivalent must be within 0.25D of the full anisometropic difference correction
- Astigmatism cylinder must be within 0.25D of full correction and axis must be within 5 degrees of full correction.

- For hyperopia and myopia, the spherical component can be reduced by investigator discretion provided the reduction is symmetrical and results in residual (i.e., uncorrected) spherical equivalent refractive error that does not exceed +3.50 D spherical equivalent hyperopia or -0.50 D spherical equivalent myopia.
- Deliberate over-minus using refractive correction with more than 0.50 D of over-minus will not be allowed. However, not prescribing the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overminusing for this protocol and is therefore allowed. It should be noted on the data collection form whether the amount of hyperopic correction is deliberately being manipulated to better control the IXT.

4.4 Strabismus Surgery

Strabismus surgery is not allowed during the study before the 3-month masked exam and is only allowed thereafter if specified deterioration criteria are met (*section 3.4*). The reason for performing surgery should be recorded in the comment section of the Follow-up Examination Form.

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 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 for a patient treated with occlusion therapy 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. In cases of persistent skin irritation with adhesive patches, children will be asked to wear a non-adhesive patchwork patch over spectacles (if wearing spectacles) or a 'pirate' patch if not wearing spectacles.

- In rare instances patching can cause a decrease in the visual acuity in one eye, although this is almost always reversible. This occurrence is extremely unlikely in view of the low number of hours of daily patching, unless treating amblyopia, where the risk is still extremely low.

4.5.3 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.

4.6 Reporting of Adverse Events

Any development of amblyopia or reverse amblyopia during the study 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.

4.7 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.

4.8 Travel Reimbursement

The parent of each patient will be compensated $30 per visit for completion of each study-mandated follow-up exam, up to a maximum of $210. If there are extenuating circumstances, and the patient is unable to complete study visits without additional funds due to travel costs, additional funds may be provided.

4.9 Study Costs

The subject or his/her insurance will be responsible for the costs that are considered standard care. This includes the initial examination, all follow up visits except the 3-month visit, any non-surgical treatments other than patching, any surgical procedures, and any costs involved in managing surgical complications.

Patients prescribed patching will be provided patches by the study at no cost.

The study will not pay for spectacles required at enrollment, but will pay for lens changes and/or new spectacles that are needed during follow up to keep the correction within the study guidelines *(section 4.3).* All other new spectacles and/or lens changes will not be paid for by the study, as they are part of normal care. The study will not pay for contact lenses.

CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

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

5.1 Objective #1: Treatment Efficacy

Objective #1 is to determine the efficacy of occlusion treatment.

5.1.1 Primary Analysis

The primary analysis for treatment efficacy will be to perform a treatment group comparison of the proportion of patients meeting deterioration criteria at 6 months among patients the primary cohort consisting of patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest.

A one-sided Z-test with alpha = 0.05 will be used to perform a treatment group comparison of the proportion of patients who meet the criteria for deterioration at the 6-month outcome exam (*section 5.1.1.1*). A 95% confidence interval on the difference of proportions between the two groups also will be calculated.

The primary analysis will follow the intent-to-treat principle. Rubin's multiple imputation[19] will be used to impute an outcome for patients who are lost to follow-up or withdraw from the study prior to the 6-month exam. Although loss to follow up by 6 months is expected to be low, secondary analyses will be conducted using the last-observation-carried-forward for deterioration status for patients who completed the 3-month exam but did not complete the 6-month exam. Additional secondary analyses to be conducted are two complete case analyses—one including only patients who completed the 6-month year visit and the other including only patients whose 6-month outcome exams were performed within the time window for the visit. If secondary analyses yield similar results to the primary analysis, they will be used to provide supportive evidence for the primary analysis conclusion. If results differ, exploratory analyses will be conducted to evaluate the reasons for the difference.

5.1.1.1 Classification of 6-month Outcome

At the 6-month visit, each patient's condition will be classified as either deterioration, success, or indeterminate as follows:

Deterioration: ANY of the following criteria are met BY the 6-month visit:

1. Constant exotropia at least 10 PD at distance **AND** near (throughout exam) by SPCT, confirmed by a retest
2. Drop in near stereoacuity by Preschool Randot stereotest of at least 2 octaves (at least 0.6 log arcsec) from *baseline* stereoacuity (*see Table 1*), or to nil, confirmed by a retest
3. Surgical or nonsurgical treatment for IXT has been received (other than occlusion in the occlusion group)

Success: ALL of the following criteria are met AT the 6-month visit:

1. Exodeviation (tropia or phoria) less than 10 PD at distance and near by PACT AND reduction of >10 PD from largest baseline angle by PACT
2. Esotropia less than 6 PD by PACT

3. No drop in near stereoacuity by Preschool Randot stereotest of at least 2 octaves (at least 0.6 log arcsec) from baseline stereoacuity measurement (*see Table 1*), and no drop to nil
4. No surgical or nonsurgical treatment for IXT has been received other than occlusion in the occlusion group

Indeterminate: ALL of the following criteria are met AT the 6-month visit:

1. Patient meets one or more of the following:
   - Constant exotropia >=10PD at only one distance (i.e. at distance or near but not both)
   - Intermittent exotropia >=10PD at distance and/or near
   - Exodeviation (tropia or phoria) less than 10 PD at distance and near by PACT but no reduction of >10 PD from largest baseline angle by PACT
   - Esotropia >=6PD by PACT at distance or near
2. No drop in near stereoacuity by Preschool Randot stereotest of at least 2 octaves (at least 0.6 log arcsec) from baseline stereoacuity measurement (*see Table 1*), or to nil, that was confirmed by a retest
3. No surgical or nonsurgical treatment for IXT has been received other than occlusion in the occlusion group

5.1.2 Secondary Analyses

All secondary treatment efficacy analyses are limited to patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest.

5.1.2.1 Deterioration at 3 Months

A treatment group comparison of proportions of patients who meet the criteria for deterioration (*section 3.4*) by the 3-month outcome exam will be performed using a Fisher's exact test. A 95% confidence interval on the difference of proportions of patients meeting deterioration criteria between the two groups also will be calculated. Deterioration will be classified as in the 6-month primary analysis (*section 5.1.1.1*). Data will be included only from patients who complete the 3-month exam.

5.1.2.2 Deterioration at 6 Months in Subgroups

The 6-month treatment effect in subgroups based on baseline factors will also be assessed in a secondary analysis. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. Subgroup analyses will be interpreted with caution, particularly in the absence of an overall treatment group difference.

The primary subgroups of interest are baseline monofixation status as determined using Titmus stereoacuity data, baseline monofixation status determined as using Preschool Randot stereoacuity data, age at randomization, and baseline IXT type. Other baseline factors which will be assessed in exploratory subgroup analysis are near stereoacuity, distance stereoacuity, control of IXT, whether a constant exotropia was present at distance at enrollment, and quality of life. In accordance with NIH guidelines, a subgroup analysis of treatment efficacy according to gender, as well as race/ethnicity, will also be conducted.

The general approach for subgroup analyses will be to determine the proportion of patients with deterioration for each treatment group within each subgroup, using the same method as for the primary analysis. Factors showing evidence of interaction with treatment effect will be formally

assessed by including an interaction term in a logistic regression model that includes the factor. In general, power will be low for formally detecting an interaction unless the interaction is very large.

5.1.2.3 Treatment Success at 6 Months

A treatment group comparison of proportions of patients who meet the criteria for treatment success by the 6-month outcome exam (*section 5.1.1.1*) will be performed using a Fisher's exact test. A 95% confidence interval on the difference of proportions between the two groups also will be calculated.

5.1.2.4 Other Secondary Outcomes at 6 Months

Additional secondary analyses will be performed to assess whether 6-month treatment group differences exist in outcomes of ocular alignment, control of IXT, near stereoacuity, distance stereoacuity, monofixation status determined using Titmus stereoacuity data, monofixation status determined using Preschool Randot stereoacuity data, development of amblyopia and/or quality of life. Details of these analyses will be outlined in the detailed statistical analysis plan.

5.1.3 Exploratory Analyses

5.1.3.1 Patients Unable to Measure Stereoacuity at Baseline

An exploratory objective will assess the 6-month treatment efficacy in a secondary cohort of patients who are too young to perform Preschool Randot Stereoacuity testing at baseline. This cohort will be comprised of all patients aged 1 to < 3 years and those patients aged 3-4 years who do not understand the Preschool Randot Stereotest well enough to complete it at baseline.

A Fisher's exact test will be used to perform a treatment group comparison of the proportion of patients who have a constant exotropia at least 10 PD by SPCT at distance and near at the 6-month exam. A 95% confidence interval on the difference in proportions between treatment groups will also be calculated. Patients receiving surgical or non-surgical treatment for IXT (other than occlusion in the occlusion group) before 6 months will also be counted as having a constant exotropia at least 10 PD by SPCT at distance and near. All other patients will be classified according to whether they have a constant exotropia at least 10 PD by SPCT at distance and near at the 6-month follow-up visit, regardless of whether it was present at an earlier visit. Data will be included only from patients who complete the 6-month exam.

5.1.3.2 Patients 3 to < 11 Years Old with Baseline Stereo 800 or Worse

Two exploratory objectives will be to assess outcomes in a secondary cohort comprised of patients aged 3-<11 years who have 800 arcsec or nil stereoacuity at near by the Preschool Randot stereotest at baseline but who were able to understand the test.

The first exploratory objective is to assess the 6-month treatment efficacy in this cohort. A Fisher's exact test will be used to perform a treatment group comparison of the proportion of patients who have a constant exotropia at least 10 PD by SPCT at distance and near at the 6-month outcome exam. A 95% confidence interval on the difference of proportions between the two groups also will be calculated. Patients receiving surgical or non-surgical treatment (other than occlusion in the occlusion group) before 6 months will also be counted as having a constant exotropia at least 10 PD by SPCT at distance and near at the 6-month exam.

The second exploratory objective will be to assess stereoacuity outcomes by 6 months. Because patients with nil Preschool Randot near stereoacuity at baseline are not at risk for a decrease in stereoacuity unless they first demonstrate stereoacuity improvement, stereoacuity outcomes will simply be enumerated in each treatment group.

5.2 Objective #2: 3 Year Outcomes Stratified By Treatment Group

Objective #2 is to evaluate 3 year outcomes for each treatment group separately.

5.2.1 Primary Analysis

The primary analysis is to determine for each treatment group the proportion of patients who meet deterioration criteria by 3 years among patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest. Of particular interest is this proportion in the observation group, the group which addresses the natural history of intermittent exotropia.

Patients will be considered to have had their condition deteriorate if they meet any of the deterioration criteria in *section 3.4*. Patients receiving surgical or non-surgical treatment for IXT (other than occlusion in the occlusion group) before 3 years will also be counted as having deteriorated. The cumulative proportion of patients meeting criteria for deterioration by 3 years will be obtained using the Kaplan-Meier method. This will allow patients who drop out prior to 3 years to contribute to the estimation of the proportion of deterioration at 3 years. In this analysis, all patients who meet deterioration criteria prior to 3 years will be counted as deteriorated at the first visit at which deterioration criteria are met.

In addition, the proportion of deteriorations at the 3 year timepoint will be estimated using the binomial proportion of patients who meet deterioration criteria at the 3 year visit. Rubin's multiple imputation[19] will be used to impute an outcome for patients who do not return for the 3 year visit. Patients who complete the visit will be classified based on their status at 3 years, regardless of whether they met deterioration criteria at an earlier timepoint, unless they have been re-operated or have initiated non-surgical treatment (other than occlusion in the occlusion group), in which case they will be classified as having deteriorated. To investigate the sensitivity of this analysis to the classification of dropouts, analyses using alternate assumptions regarding the dropouts also will be performed. Methods to be assessed include imputing data using the last-observation-carried-forward for deterioration status, and complete case analysis that includes only patients who completed the 3 year visit. If secondary analyses yield similar results to the primary analysis, they will be used to provide supportive evidence for the primary analysis conclusion. If results differ, exploratory analyses will be conducted to evaluate the reasons for the difference.

Note that although the proportion of patients with deterioration at 3 years will be calculated separately for each treatment group, a 3-year treatment group comparison is not planned. The rationale for not performing such an analysis is that the stereoacuity component of deterioration over 3 years must be assessed based on a decrease from *the best previous stereoacuity* (i.e., a post-baseline factor) in order to capture deterioration in patients whom stereoacuity improves but later worsens. Because occlusion may affect stereoacuity, the distribution of best previous stereoacuity may differ between treatment groups, thus compromising the validity of a treatment group comparison at 3 years.

5.2.1.1 Classification of 3-year Outcome

At the 3-year visit, each patient's condition will be classified as either deterioration, success, or indeterminate according to the method for the primary analysis (*section 5.1.1.1*) with the following exception: the stereoacuity component of the outcome requires a decrease in Preschool Randot near stereoacuity of at least 2 octaves from *best previous stereoacuity* at any visit including enrollment, or to nil.

5.2.2 Secondary Analyses

5.2.2.1 Association of Baseline Factors with Deterioration at 3 Years

For each treatment group separately, analyses will be performed to assess whether the proportion of patients who have deteriorated by 3 years differs according to baseline factors among patients aged 3 to < 11 years at enrollment who have near stereoacuity of 400 arcsec or better by Preschool Randot stereotest at enrollment.

The primary factors of interest are baseline monofixation status (determined using Titmus stereoacuity and Preschool Randot stereoacuity), age at randomization, and baseline IXT type. Other baseline factors which will be assessed in exploratory subgroup analysis are near stereoacuity, distance stereoacuity, control of IXT, whether a constant exotropia was present at distance at enrollment, and quality of life.

Logistic regression modeling will be used to assess whether any baseline factors are associated with the proportion of patients with deterioration.

5.2.2.2 Treatment Success at 3 Years

For each treatment group separately, a 95% confidence interval will be calculated on the proportion of patients who meet criteria for 'success' at the 3-year outcome exam (*section 5.2.1.1*) among patients aged 3 to < 11 years at enrollment who have near stereoacuity of 400 arcsec or better by Preschool Randot stereotest at enrollment.

5.2.3 Exploratory Analyses

5.2.3.1 Patients Unable to Measure Stereoacuity at Baseline

An exploratory objective will be to assess the proportion of patients experiencing deterioration by 3 years (*section 5.2.1.1*) in a secondary cohort of patients who are too young to perform Preschool Randot Stereoacuity testing at baseline. This cohort will be comprised of all patients aged 1 to < 3 years and those patients aged 3-4 years who do not understand the Preschool Randot Stereotest well enough to complete it at baseline. For each treatment group, a 95% confidence interval will be calculated on the proportion of patients who have deteriorated by 3 years. For this analysis, the stereoacuity component of the deterioration criteria applies only once a patient has had at least two visits at which stereoacuity was able to be performed.

5.2.3.2 Patients 3 to < 11 Years Old with Baseline Stereo 800 or Worse

Two exploratory objectives will assess outcomes in a secondary cohort comprised of patients aged 3-<11 years who have 800 arcsec or nil stereoacuity at near by the Preschool Randot stereotest at baseline but who were able to understand the test.

The first exploratory objective in this cohort is to assess the proportion of patients in each treatment group who have a constant exotropia at least 10 PD by SPCT at distance and near by 3 years. For each treatment group, a 95% confidence interval will be calculated on the proportion.

The second exploratory objective will assess stereoacuity outcomes at 3 years. Because patients with nil Preschool Randot near stereoacuity at baseline are not at risk for a decrease in stereoacuity unless they first demonstrate stereoacuity improvement, stereoacuity outcomes will simply be enumerated in each treatment group.

5.3 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

1) Baseline demographic and clinical characteristics
2) Baseline data for study completers vs. non-completers
3) Compliance with occlusion in the occlusion group as evidenced by investigator impression over follow-up visits;
4) Protocol deviations

A flow chart will be constructed that accounts for all subjects. Visit completion rates will be tabulated according to treatment group for each visit. The percentage of subjects with visits completed in window, out of window, and missed for each visit will be tabulated.

5.4 Interim Analysis

This study will include an interim monitoring plan that incorporates at least one and up to three interim analyses, consisting of a treatment group comparison of proportion of patients meeting deterioration criteria at 6 months. The monitoring plan will consist of a one-sided boundary for efficacy and a one-sided boundary for futility.[20] This will allow for early stopping to be considered in the event that interim data strongly support a treatment effect favoring occlusion, or alternatively, when interim data support that a treatment effect as large as the designed effect (a 10% difference in deterioration rate favoring occlusion) is highly unlikely.

In the event of early stopping for lack of efficacy of occlusion, the proposal would be to discontinue randomizing patients but to continue enrolling patients into the observation group. This strategy would allow a sufficient number of patients to obtain the desired precision on the estimated proportion of observation group patients with deterioration by 3 years.

The details of the formal interim monitoring plan will be developed in conjunction with the DSMC and incorporated into the statistical analysis plan prior to any analysis of primary or secondary outcome data.

5.5 Sample Size

Sample size has been estimated for both primary analysis objectives.

Objective #1: There is essentially no literature on which to base our sample size estimates, as the natural history of IXT, and the effect of non-surgical treatment, have not been previously studied with any degree of rigor. Based upon a consensus of experts, we estimate that the proportion of patients with deterioration at 6 months will be approximately 5% with occlusion and 15% with observation alone. Using a the Z-test for a treatment-group comparison of the proportions of

patients meeting deterioration criteria at 6 months among patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest, given an expected difference of 10% (5% deterioration with occlusion vs. 15% with observation), 80% power, and one-sided alpha = .05, 111 patients aged 3-<11 with baseline stereoacuity of 400 or better would be needed per treatment group. Depending on the specific details of the monitoring plan approved by the DSMC, it is estimated that an additional 9 to 37 patients would be needed to maintain designed power and type I error rates accounting for the interim monitoring. Taking the larger of these numbers, and adjusting for an estimated 5% loss to follow up by 6 months, 156 patients per group would be needed to be randomized per treatment group.

Table 3: Sample Size for Treatment Group Differences in the Proportion of Patients with Deterioration at 6 Months

	Power	
Proportion of Patients with Deterioration in Each Treatment Group	**80%**	**90%**
5% in occlusion group vs. 10% in observation group	343	474
10% in occlusion group vs. 15% in observation group	540	748
5% in occlusion group vs. 15% in observation group	**111**	153

Data in Table 3 is sample size per treatment group for a one-sided Z-test of proportions with alpha = .05.

Objective #2: For determining the proportion of observation group patients with deterioration by 3 years among patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest, we don't know what the expected proportion with deterioration might be. However, because a confidence interval width of no more than ± .08 is desired, the number of observation group patients for analysis should be 151 based on a point estimate of 50%, the point estimate at which the confidence interval would be widest. Adjusting for an estimated 10% loss to follow up by 3 years, 168 patients would be needed to be randomized into the observation group.

Table 4: Sample Size for Various Half-Widths of 95% Confidence Intervals on Proportion of Observation Group Patients with Deterioration at 3 Years

Proportion of Observation Group Patients with Deterioration at 3 Years	**Half-Width of 95% Confidence Interval**					
	.05	**.06**	**.07**	**.08**	**.09**	**.10**
10%	139	97	71	55	43	35
20%	246	171	126	97	76	62
30%	323	225	165	127	100	81
40%	369	257	189	145	114	93
50%	385	267	196	**151**	119	97
60%	369	257	189	145	114	93

Data in Table 4 is the sample size needed for the observation group for the half-width of the 95% confidence interval for the proportion.

Given that 156 patients are needed per treatment group for the objective #1 analysis, and 168 patients are needed in the observation group for the objective #2 analysis, a minimum of 336 patients (168 patients per group) will be enrolled into the primary cohort (patients aged 3 to < 11 years who have baseline near stereoacuity of 400 arcsec or better by Preschool Randot stereotest), with a goal to enroll an appropriate representation of minorities.

An additional 40 patients aged 1 to < 3 years and patients aged 3-4 years who did not understand the Preschool Randot Stereotest well enough to complete it at baseline (20 per group) are expected to be enrolled as a secondary cohort during recruitment for the primary cohort. An additional 40 patients who have 800 arcsec or nil stereoacuity at near by the Preschool Randot stereotest test but who were able to understand the test (20 per group) are expected to be enrolled as an additional secondary cohort during recruitment for the primary cohort. Recruitment for the two secondary cohorts will be monitored during recruitment of the primary cohort. If a secondary cohort is enrolling fewer patients than expected, recruitment for that secondary cohort could be terminated before recruitment for the primary cohort has ended.

As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 436.

CHAPTER 6: REFERENCES

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