Signature Page

Randomized Trial of Full-Time Occlusion Therapy for Intermittent Exotropia in Children

Funded by: The National Eye Institute of the National Institutes of Health

Protocol Identifying Number: IXT7

Version Number: 1.0

19 April 2022

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KEY ROLES

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
Δ	Prism diopters
ANCOVA	Analysis of covariance
ATS	Amblyopia Treatment Study
ATS-HOTV	Amblyopia Treatment Study HOTV visual acuity testing protocol
CI	Confidence interval
CFR	Code of Federal Regulations
CR	Cycloplegic refraction
CRF	Case report form
D	Diopter
DHHS	Department of Health and Human Services
DSMC	Data safety and monitoring committee
eCRF	Electronic case report form
E-ETDRS	Electronic Early Treatment of Diabetic Retinopathy Study visual acuity protocol
EVA	Electronic visual acuity tester
FDA	Food and Drug Administration
FDR	False discovery rate
FT	Full-time patching
GCP	Good clinical practice
ICH	International Council for Harmonisation
IOD	Interocular difference
IRB	Institutional Review Board
ITT	Intention to treat
IXT	Intermittent exotropia
JCHR	Jaeb Center for Health Research
logMAR	Logarithm of the minimal angle of resolution
log sec arc	Logarithm of the seconds of arc
MCMC	Monte Carlo Markov chain
NIH	National Institutes of Health
Obs	Observation
PACT	Prism and alternate cover test
PEDIG	Pediatric Eye Disease Investigator Group
QA	Quality assurance
QC	Quality control
RBM	Risk-based monitoring
RCT	Randomized clinical trial
SAP	Statistical analysis plan
SD	Standard deviation
SE	Spherical equivalent refractive error (Sphere + ½ Cylinder)
sec arc	Seconds of arc
SPCT	Simultaneous prism and cover test
VA	Visual acuity

PRINCIPAL INVESTIGATOR AGREEMENT FOR PROTOCOL

Randomized Trial of Full-Time Occlusion Therapy for Intermittent Exotropia in Children (IXT7)

Site Number: _____

Each clinical site that is approved to participate in the IXT7 study will have one individual designated as the Protocol Principal Investigator (Protocol PI) at the site for that protocol. This may or may not be the same investigator that serves as the overall Site Principal Investigator (Site PI) for all PEDIG studies.

The Protocol PI and the Site PI (if different) agrees to the following for the IXT7 study. They will:

- Have a thorough understanding of the protocol design and study procedures.
- Ensure that local institutional requirements (if applicable) are satisfied for the protocol and that approvals and assurances are obtained annually if required.
- Ensure that the required protocol-certified staff, facilities, and equipment are available to conduct the protocol.
- Ensure that the required protocol staff have a thorough understanding of the protocol design and procedures.
- Provide adequate support and guidance to site investigators, coordinators, and other staff so that the study can be conducted according to protocol.
- Respond promptly to requests from the Coordinating Center (CC), Network Chair/s, or Protocol Chair/s.
- Correspond and maintain accessibility via email and phone with their PEDIG protocol monitor.
- Oversee local study documentation and records.
- Conduct periodic meetings of study personnel at their site.
- Cooperate with protocol monitors by working with the site coordinator to make available study personnel, study records, protocol binders, clinic charts for study participants, and other necessary records needed for on-site or virtual clinic monitoring visits.
- Notify the CC if any protocol adherence or data reporting problem is discovered or suspected.
- Attend scheduled PEDIG meetings and conference calls, including those for any PEDIG committees to which appointed.
- Review study monitoring reports evaluating clinical site performance and discuss with the CC any areas identified to be deficient.

The Protocol and PI shall exert diligent efforts to enroll at least three (3) study subjects.

In addition to the above, the Protocol PI and the Site PI (if different) agree(s) to the following:

- I/we understand the importance of successful follow-up of participants enrolled at my/our site.
- I/we agree as a site that we have the potential and commitment to as a site to enroll at least 3 subjects once certified.

Protocol Principal Investigator's Signature **Date: _____ / _____ / _____**

Name: _____

To be completed only if different:

Site Principal Investigator's Signature _____ **_____Date: _____ / _____ / _____**

Name: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Randomized Trial of Full-Time Occlusion Therapy for Intermittent Exotropia in Children
Précis	Understanding the effectiveness of intensive patching has important implications for managing children with IXT. If full-time patching is associated with improvement in distance control vs an observation group, then future studies can be conducted to evaluate different durations of full-time patching treatment, whether the effect is maintained off-treatment, and how full-time patching compares to other treatment strategies.
Objectives	Determine whether full-time patching is more effective than observation for improving distance control of IXT after 3 months of treatment (on-treatment outcome).
Study Design	Randomized clinical trial.
Number of Sites	The study is open to all clinical sites approved to participate in the PEDIG network.
Endpoint	**Primary Efficacy Outcome:** Change in control of IXT at distance after 3 months based upon the average of three measures of control at distance. **Key Safety Outcomes:** 1. Deterioration is defined as meeting one of the following criteria at the 3 months follow-up visit: • Constant exotropia >= 10Δ at distance AND near by SPCT. 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. • Decrease in near stereoacuity on the Randot Preschool Stereotest of at least 2 levels from baseline, or to nil. 2. Decrease in distance visual acuity 3 or more logMAR lines from baseline in either eye or IOD 3 or more logMAR lines. 3. Diplopia 'More than 2 times per day' by parental report 4. Diplopia 'All the Time' by child symptom survey
Population	**Inclusion Criteria:** Children under the care of a pediatric optometrist or pediatric ophthalmologist will be eligible for the study if they meet all the following criteria: 1. Age 3 to < 9 years 2. IXT meeting all of the following criteria: • Intermittent or constant XT at distance (mean distance control 2.0 or more) with at least 1 control measure of 3, 4 or 5 (i.e., indicating spontaneous tropia) • Either IXT, exophoria, or orthophoria at near (cannot have control score of 5 on all 3 near assessments) • Distance exodeviation between 15Δ and 50Δ by PACT • Near exodeviation between 0Δ and 50Δ by PACT • Near exodeviation does not exceed distance by more than 10Δ by PACT (convergence insufficiency-type IXT excluded) 3. Age-normal visual acuity in both eyes: • 3 years: 20/50 or better (>=63 letters) • 4 years: 20/40 or better (>=68 letters)

PARTICIPANT AREA	DESCRIPTION
	• 5-6 years: 20/32 or better (>=73 letters) • 7-<9 years: 20/25 or better (>=78 letters) 4. Interocular difference in distance VA of 2 logMAR lines or less (10 letters or less on E-ETDRS for patients ≥7 years old). Testing by ATS HOTV for participants 3 to < 7 years old and by E-ETDRS for participants ≥7 years old. 5. Cycloplegic refraction within the last 7 months. 6. Refractive error between -6.00 D SE and +2.00 D SE (inclusive) based on a cycloplegic refraction within 7 months 7. Participants with refractive error meeting any of the following based on a cycloplegic refraction within 6 months must be wearing spectacles for at least 2 weeks: • Myopia > -0.50 D spherical equivalent (SE) in either eye • Anisometropia > 1.00 D SE • Astigmatism in either eye > 1.00 D 8. Any refractive correction worn at enrollment (required or not) must meet the following guidelines based on a cycloplegic refraction within 7 months: • Anisometropia SE must be within 0.50 D of the full anisometropic difference correction • Astigmatism must be corrected within 0.50 D • Axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D. • For hyperopia, the spherical component can be reduced at investigator discretion provided the reduction is symmetrical and does not meet the definition of deliberate overminus (see below). • For myopia, the intent is to fully correct, but the spherical component can be undercorrected at investigator discretion provided the reduction is symmetrical and results in no more than -0.50 D SE residual (i.e., uncorrected) myopia. Deliberate overminus is not allowed. • Deliberate overminus is defined for this protocol as any refractive correction prescribed to yield lenses that are overminused by more than -0.50D SE than cycloplegic refraction SE ▪ Less than the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overminusing for this protocol (because most patients without IXT but with hyperopic SE refractions up to +2.00 D SE would not typically be prescribed a refractive correction.) • For refractive errors with an emmetropic or myopic SE, the intent is to fully correct, but the spherical component can be undercorrected at investigator discretion provided the reduction is symmetrical and results in no more than -0.50 D SE residual (i.e., uncorrected) myopia. Prescribing a correction that yields more than 0.50 D *more minus* SE than the cycloplegic refraction SE is considered deliberate overminus and is not allowed. • Note that the refractive correction guidelines and the requirement to wear refractive correction for at least 2 weeks apply not only to participants who require refractive correction under the above criteria but also to any other participant who is wearing refractive correction. 9. Gestational age > 30 weeks 10. Birth weight > 1500 grams 11. Patient and/or parent understands protocol, is willing to enroll, and is willing to accept that other (i.e., nonrandomized) treatment for IXT will not be offered by the investigator for 3 months 12. Parent has phone and is willing to be contacted by Jaeb Center staff 13. Relocation outside of area of an active PEDIG site within 3 months

PARTICIPANT AREA	DESCRIPTION
	not anticipated **Exclusion Criteria:** Individuals meeting any of the following criteria at baseline will be excluded from study participation: 1. Prior strabismus, intraocular, or refractive surgery (including BOTOX injection) 2. Prior nonsurgical treatment for IXT (e.g., patching, vergence therapy, vision therapy/orthoptics, base-in prism, or deliberate overminus (more than 1.00 D) spectacles of >1week duration within the past year 3. Previous amblyopia treatment other than refractive correction 4. Diplopia more than 2 times per day by parental assessment 5. Paretic or restrictive strabismus 6. Craniofacial malformations affecting the orbits 7. Ocular disorders which would reduce VA (except refractive error) 8. Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Participants with mild speech delay or reading and/or learning disabilities or ADHD are not excluded. 9. Neurological anomaly that could affect ocular motility (e.g., cerebral palsy, Down syndrome) 10. Immediate family member (child or sibling) of any investigative site personnel directly affiliated with this study. 11. Known allergy to adhesive patches. 12. Known allergy to silicone.
Sample Size	72 (36 observation, 36 full-time patching)
Phase	Phase 3
Treatment Groups	Random assignment to: • Observation • Full-time patching (all waking hours, 7 days/week)
Participant Duration	3 months after randomization
Protocol Overview/Synopsis	Participants will be randomly assigned to observation or full-time patching. All parents will receive a phone call at 4 weeks to answer any questions about observation or patching treatment. Participants will be followed for 3 months.

STUDY SUMMARY FLOW CHART

Major Eligibility Criteria

- Children aged 3 to <9 years
- Intermittent exotropia meeting all the following criteria:
  - Intermittent or constant XT at distance (mean distance control 2.0 or more, with at least 1 measure of 3, 4 or 5
  - IXT or exophoria or orthophoria at near (cannot have control score of 5 on all 3 near assessments)
  - Distance deviation between 15Δ and 50Δ by PACT
  - Near deviation between 0Δ and 50Δ by PACT
  - Near deviation does not exceed distance by more than 10Δ by PACT
- No prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- No previous nonsurgical treatment of >1 week duration within the past year
- No amblyopia treatment other than refractive correction
- No diplopia more than 2 times per day by parental report
- Refractive error between -6.00 D SE and +2.00 D SE (inclusive) based on a cycloplegic refraction within 7 months
- Age-normal VA (3 yrs = 20/50 or better; 4 yrs = 20/40 or better; 5-6 yrs = 20/32 or better; 7-8 yrs = 20/25 or better)
- No interocular VA difference more than 0.2 logMAR
- Wearing appropriate refractive correction for at least 2 weeks
- No abnormality of the cornea, lens, or central retina
- No known allergy to adhesive patches or silicone.

↓

Enrollment/Baseline Visit

- Informed consent
- Pediatric Eye Questionnaire (PedEyeQ)
- IXT Symptom Survey
- Diplopia Assessment by Parent
- Randot Preschool Stereoacuity (40 cm)
- Exotropia control #1 (distance and near)
- Divergence and convergence fusional amplitudes
- Exotropia control #2 (distance and near)
- Ocular alignment (cover/uncover, SPCT, PACT)
- Exotropia control #3 (distance and near)
- Suppression
- Retinal correspondence (ages 6-8 years)
- Assessment of eligibility

↓

Randomize

↙ ↘

Observation | Patching All waking hours

↓

4 weeks (± 1 week): Phone Call

↓

3 months (±2 weeks) Primary Outcome

- Patch adherence monitoring (patching group only)
- Pediatric Eye Questionnaire (PedEyeQ)
- IXT Symptom Survey
- Diplopia Assessment by Parent
- Randot Preschool Stereoacuity (40 cm) (masked)
- Exotropia control #1 (distance and near) (masked)
- Divergence and convergence fusional amplitudes (masked)
- Exotropia control #2 (distance and near) (masked)
- Ocular alignment (cover/uncover, SPCT, PACT) (masked)
- Exotropia control #3 (distance and near) (masked)
- Suppression (masked)
- Retinal correspondence (ages 6-8 years) (masked)

SCHEDULE OF STUDY VISITS AND PROCEDURES

	Enrollment	4-Week Call	3-Month Visit
Consent	X		
Demographics / Medical History	X		
Treatment Compliance		X	X
Quality of Life Survey	X		X
IXT Symptom Survey	X		X
Diplopia Assessment by Parent	X		X
Distance Visual Acuity	X		X
Randot Preschool Stereoacuity	X		X
Exotropia Control (distance and near)	X		X
Amplitude Testing (Divergence and Convergence)	X		X
Ocular Alignment (distance and near)	X		X
Suppression (distance)	X		X
Retinal Correspondence*	X		X

[a] Retinal correspondence to be measured only in children 6, 7, or 8 years of age at randomization

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Chapter 1: Background Information

1.1 Epidemiology and Clinical Characteristics

Intermittent exotropia (IXT) is the most common form of childhood-onset exotropia,[1,2] with an incidence of 32.1 per 100,000 in children under 19 years of age,[1] and occurring more frequently in females[3] and in Asian populations.[4-6] Onset of IXT is thought to be in the first year of life.[7] Etiology is unknown although anatomical, innervational, sensory, and genetic factors have been proposed.[8,9]

IXT is characterized by an exodeviation present predominantly at distance fixation with or without deviation at near fixation. Pseudonyms include periodic exotropia and exotropia of inattention. In addition to being present for distance viewing, exotropia may also occur at near and with inattention, in bright sunlight, or when tired. Closure of one eye in bright sunlight and sensitivity to sunlight[10-12] are also characteristic features. Normal binocular single vision is typically present at near when the eyes are aligned, with normal (occasionally subnormal) stereoacuity.[13,14] Diplopia is rarely reported.[15]

IXT is characterized by unique sensory adaptations:[16] suppression mechanisms prevent diplopia when the exodeviation is manifest, but normal binocular single vision with normal stereoacuity is reestablished when the deviation is controlled (albeit with persistent temporal retinal suppression in some children[17]). In addition, some children with IXT are thought to covary between normal and anomalous retinal correspondence (ARC)[16,18] and may also experience panoramic viewing.[7,19] However. the true nature of these adaptations, how often they occur, and how they respond to treatment are poorly characterized having not been previously studied in large numbers of children with IXT.

1.2 Current Management Strategies

IXT is currently managed by observation alone, or with surgical correction or non-surgical treatment.[14] Despite a plethora of studies evaluating treatments for IXT, there are relatively few data on treatment effectiveness[14] and current practice patterns are fragmented.[20,21]

In addition, long-term success following treatment appears elusive, and specific reasons for treatment failure are unclear. Popular explanations include the possibility that persistent sensory maladaptations (suppression and/or anomalous retinal correspondence), as well as inadequate fusional amplitudes, may be responsible for recurrence of the exotropia following treatment.

To provide context for the proposed randomized clinical trial (RCT), the following summary briefly describes commonly used management strategies along with data from previous RCTs.

1.2.1 Observation

We are aware of two previous RCTs in which subjects with IXT were randomized to observation. The PEDIG IXT2 studies[22,23] randomized children to observation versus part-time patching. In the older cohort randomized to observation (3 to < 10 years at enrollment), deterioration of IXT (constant exotropia ≥10Δ at distance and near or ≥2-octave decrease in near stereoacuity from the best previous measure, or being prescribed treatment despite not having met motor or stereo deterioration) was met in 25 of 183 by 3 years (15%, 95% confidence interval = 10%-22%), 12 of whom were prescribed treatment without meeting motor or stereoacuity criteria.[24] However, of the 132 who completed the 3-year visit and had not been

treated during the study, only 1 (<1%) met motor or stereoacuity deterioration criteria at 3 years.[24] Of those older children randomized to observation who remained untreated over the 3 years, "complete or near complete resolution" (exodeviation <10Δ at distance and near, no reduction in stereoacuity, and no other nonsurgical treatment for IXT, having never met deterioration criteria) was met in 6 (7%) of 86.[25]

In the younger cohort randomized to observation (12-35 months at enrollment), deterioration of IXT (constant exotropia ≥10 prism diopters at distance and near or treatment prescribed despite not having met motor deterioration) occurred in 28% (95% CI = 20%–39%) by 3 years.[26] Of the 24 participants meeting the primary outcome of deterioration, seven met motor deterioration and 17 were prescribed treatment without meeting motor deterioration.[26] The cumulative probability of motor deterioration by 3 years was 10% (95% CI = 5%–19%).

In a pilot RCT of surgery versus observation for IXT, Clarke et al[27] found 2 (9%) of 22 in the observation group showed significant improvement in control (improved 3 and 4 points on the office control scale) after 9 months of follow-up.

1.2.2 Surgery

The aim of surgery for IXT is to reduce the magnitude of the exodeviation (or eliminate it completely) such that any residual deviation can be easily compensated by existing convergence and divergence motor fusion mechanisms. Two RCTs have evaluated surgery for IXT.[14] PEDIG (IXT1)[28] compared bilateral and unilateral surgery and found complete or near-complete resolution of IXT in 30% of participants overall at 3 years postoperatively (complete or near complete resolution defined as exodeviation <10Δ at distance and near, reduction of ≥10 Δ by PACT, esotropia <6Δ by SPCT at distance and near, no ≥2 octave reduction in stereoacuity, no reoperation, no nonsurgical treatment for recurrent or residual exodeviation, and having never met failure criteria [exotropia ≥10Δ by SPCT at distance or near, constant esotropia ≥6Δ by SPCT at distance or near, and ≥2 octave reduction in stereoacuity]). In a separate RCT, Kushner[29] also compared unilateral versus bilateral surgery and found a satisfactory outcome (aligned within 10Δ of exophoria and 5Δ of esophoria) in 82% and 52% respectively, but outcomes were evaluated at only one year postoperatively. In IXT1,[30] younger age (3 to <5 years) was associated with a lower risk of failure by 3 years (28% vs 50%); however, reasons for failure versus success were not explored in Kushner's RCT.

1.2.3 Nonsurgical treatments

The aim of nonsurgical treatment for IXT is to improve the strength and/or quality of binocular single vision (reducing suppression, increasing fusional amplitudes), thereby improving control of the exodeviation. Commonly utilized non-surgical management strategies include, vision therapy, overminus lenses, relieving or correcting base-in prism, and part-time patching.

Vision therapy:

There are no published RCTs of vision therapy, but a multicenter pilot RCT is planned and due to commence in 2021 (NCT04487249).

Overminus optical correction:

A recently published RCT (IXT5; NCT02807350) conducted by PEDIG,[31] randomized 3- to 10-years old with IXT to overminus spectacles (−2.50 D over cycloplegic refraction for 12 months) vs non-overminus spectacles and found better mean distance control at 12 months (in correction)

for participants treated with overminus spectacles (n=196) than those with non-overminus spectacles (n=190) (1.8 vs 2.8 points; adjusted difference, −0.8; 95% CI, −1.0 to −0.5; *P*< 0.001). Factors associated with better versus worse control at outcome were not evaluated. However, a greater myopic shift occurred in those with overminus vs non-overminus treatment (−0.42 D vs −0.04 D; adjusted difference, −0.37 D; 95% CI, −0.49 to −0.26 D; *P*<0.001), resulting in the overminus spectacles being discontinued before follow-up was complete in some participants.[31]

Prism correction:
Relieving base-in prism correction was evaluated in an 8-week pilot RCT conducted by PEDIG (IXT6; NCT03998670). The primary outcome was change in exodeviation control score, but factors associated with success versus failure of treatment were not evaluated. Results are due to be published later this year.

Patching:
Patching is one of the most frequently prescribed nonsurgical treatments for IXT and is described in detail below (section 1.3).

1.3 Patching

1.3.1 Current clinical practice

Prevailing clinical practice is to prescribe a low dose of 2-4 hours/day, and to either patch alternate eyes, alternate days, or patch the eye preferred for fixation (if present). Some clinicians prescribe for longer periods of time such as 6-8 hours/day or full-time (all waking hours) based on their clinical experience or outcomes from previous full-time patching studies,[32,33] but there is no evidence to support whether full-time patching has additional benefit to part-time patching. Patching may be prescribed over a short duration of weeks or months or may be utilized on and off over a period of years. It is currently prescribed either to improve exodeviation control to the point where other treatments are not necessary, or to maintain reasonable control until the child and family are ready for other treatments such as surgery or vision therapy. While patching therapy is thought to improve exodeviation control and potentially reduce the size of the exodeviation, there are few data on the magnitude of such effects or whether any benefit persists long-term.

1.3.2 Previous Randomized Trials of Patching Treatment

Akbari et al 2020[34]: Akbari et al recently published a RCT[34] comparing part-time patching (2 hours a day, alternating eyes) to observation in 76 children who were 3- to 8-years-old with IXT. The primary outcome was a single measure of control, using a modification of the Office Control Score[35] at 3 and 6 months (on treatment). Control scores ranged from 0 (phoria) to 6 (constant exotropia) and were better (lower score) in the patching group at 3 months (distance: 2.3±1.0 points vs 2.7±1.1 points; *P*=0.03; near: 1.2±0.7 points vs 1.5±0.6 points; *P*=0.003), and at 6 months (distance: 2.4±1.1 points vs 2.8±1.2 points; *P*=0.03; near: 1.0±0.6 points vs 1.6±0.9 points; *P*=0.003). Nevertheless, post-treatment outcomes, as well as effects on suppression, angle of deviation, and fusional amplitudes were not evaluated. In addition, while control improved with patching, control scores reflect that many participants had persistent intermittent exotropia.

PEDIG 2014[22] and PEDIG 2015[23]: Two PEDIG RCTs evaluated part-time patching (3 hours a day for 5 months) versus observation in 12- to 35-month-olds[23] and 3- to <11-year-olds[22] with IXT. In published secondary analyses of 6-month outcomes (1-month post cessation of patching

treatment), mean control scores and mean angle of deviation were compared between patching and observation groups. For 12- to 35-month-olds, mean distance control scores were better (lower) in the patching group compared with the observation group (2.3 points vs 2.8 points; *P*=0.02) (near control scores were similar: 1.1 points vs 1.4 points; *P*=0.26).[23] In addition, mean distance angle of deviation (PACT) was significantly smaller in the patched group (24.9Δ vs 27.9Δ, *P*=0.02)(near angle was similar: 17.0Δ vs 19.3Δ, *P*=0.10). For 3- to <11-year-olds, distance control scores were similar between groups (2.0 points patching vs 2.3 points observation; *P*=0.094) but near control scores were lower in the patching group (0.9 points vs 1.2 points; *P*=0.013).[22] Mean angle of deviation by PACT was 22.2Δ in the patching group vs 23.8Δ in the observation group (P=0.012) at distance and 15.4Δ vs 17.6Δ (*P*=0.11) at near.

The studies were designed primarily to evaluate deterioration rates, but in post hoc analyses (publication in process) of 3- to <11-year-olds with a control score of 2 or more at enrollment and a 3-month on-treatment examination (matching current study inclusion criteria and primary outcome time-point) distance control improved 0.4 points in the observation group (n=147) and 0.8 points in the patching group (n=125) (mean difference 0.41 points (95% CI, 0.12 to 0.70 points). Angle of deviation improved 0.2Δ in the observation group and 2.3Δ in the patching group (mean difference 2.1Δ (0.6 to 3.6Δ).

Nevertheless, in both the 12- to 35-month and 3- to <11-year-old cohorts, many participants had persistent intermittent exotropia post-treatment. Changes in suppression or fusional amplitudes, and relationships with better versus worse control, were not evaluated.

1.3.3 Previous Non-randomized Studies of Patching Treatment

A small number of non-randomized studies have evaluated patching for IXT.[16,36,37] While there are intrinsic challenges when interpreting data from non-randomized studies, the following are selected for more detailed review either because they provide additional information on potential effects of full-time patching, and/or provide some insight regarding how patching may impact sensory adaptations, the angle of deviation, or fusional amplitudes.

Full-time Patching

Iacobucci & Henderson 1965[33]: Twenty-eight children with IXT, scheduled for surgery, were selected ("at random") for full-time patching for 3 months. IXT control and angle of deviation were compared with a control group of 38 children undergoing anti-suppression and diplopia therapy. Distance angle of deviation by PACT reduced by a mean of 5.8±1.1Δ from baseline to 3 months in the patching group, compared with an increase of 1.8±0.4Δ in the control group. Near angle of deviation by PACT reduced by a mean of 4.6±1Δ from baseline to 3 months in the patching group, compared with an increase of 1.3±0.5Δ in the control group. Eleven of 28 patched patients and 20 of 38 control patients were constant exotropia at distance at baseline; of these, 8 (73%) of 11 in the patching group and 0 of 20 in the control group became intermittent or phoric at 3 months.

Flynn et al 1976[32]: In a prospective study, Flynn and colleagues prescribed full-time patching for 4-12 weeks to 31 children (mean age 7.6 years, range 3 to 13 years) with IXT. Mean angle of deviation pre-treatment was 20±7Δ at distance and 15±12Δ at near. Nine of 31 had undergone previous surgery. Following patching treatment, 7 (23%) of 31 showed dramatic improvement such that "the deviation became almost completely phoric, fusion improved, and all evidence of suppression on the synoptophore or in free space disappeared." Fourteen of 31 patients had a reduction in angle of deviation and a change from tropia to intermittent tropia or phoria. In 12 of

31 patients there was a measurable improvement in suppression with disappearance of the suppression scotoma. Increase in the range of fusional amplitudes occurred in 9 of these 12 patients. Of note, Flynn et al[32] report that some patients did not respond positively to patching, with 12 showing an increase in angle of deviation (mean 5Δ, range 2Δ to 15Δ) and 6 showing worsening control. Long-term follow-up was not reported.

1.4 Mechanism of Patching Treatment Effect

Patching is considered "anti-suppression" therapy, affecting exodeviation control by reducing or eliminating the suppression that occurs when the exodeviation is manifest.[32,33,38,39]

1.4.1 Suppression

Previous studies have attempted to evaluate the presence versus absence of suppression, as well as the size and location of the suppression scotoma when the exodeviation is manifest,[15,18,40-44] but few have evaluated changes in suppression with treatment or the relationship between suppression status and treatment success. In fact, although patching is designated "anti-suppression" treatment, there are few data demonstrating that changes in suppression occur with patching.

It has been suggested that, left untreated, suppression in many children with IXT will increase,[41] making it harder to remediate and leading to poorer treatment outcomes, but this has not been studied. It has also been suggested that eradication of suppression is required for successful treatment,[15] but this deserves further study.

1.4.2 Fusional Vergence Amplitudes

Motor fusion mechanisms are responsible for maintaining binocular alignment, and in IXT, both convergence and divergence are thought to be important for enabling motor control of the exodeviation.[45,46] In previous studies,[32,38,47,48] data suggest that patching results in an increase in convergence amplitudes, but further study is needed to verify whether such changes truly occur and if they do, whether they are directly related to changes in suppression or occur independently. It is also unknown how such changes relate to improvement or successful treatment of IXT.

1.4.3 Magnitude of Deviation

Previous studies[22,23,32,33,39,48-50] have shown that the magnitude of the deviation may reduce with patching treatment. Nevertheless, there are few data that support this notion, and the mechanism by which patching might alter ocular alignment remains unclear.

1.5 Measuring Patch Wear Time

Adherence with a prescribed patching dose is often problematic and limits the interpretation of findings when attempting to correlate dose to outcome. In studies of patching treatment for amblyopia, some research groups have used occlusion dose monitors (ODMs) to record actual patch wear time.[51-54] In general these previous studies concluded that dose is a significant factor in determining amblyopia treatment outcome, although there remains considerable individual variability. We are unaware of previous studies that have analyzed actual patch wear time when treating IXT, and such data are important for understanding whether there is a dose effect relationship.

Recently, a new method of monitoring patching adherence has become available and is being used in a concurrent PEDIG amblyopia study (ATS22, NCT04378790). TheraMon®, a

thermosensor device, appears to work well for monitoring adherence with amblyopia patching treatments in children.[51] We propose utilizing the TheraMon® in the current study to enable important secondary analyses of outcome in relation to actual (rather than prescribed) wear time.

1.6 Unanswered Questions Regarding Patching Treatment for IXT

While previous data confirm an effect of patching on control of IXT, and even on angle of deviation, there remain many unanswered questions regarding treatment effectiveness. Such questions include:

- Is prescribed full-time patching more effective for improving control and/or reducing angle of deviation than observation alone?
- Does patching alter suppression, angle of deviation, fusional amplitudes, or anomalous retinal correspondence, and are such changes related to exodeviation control?
- Is there a dose-response relationship (greater improvement with more actual patching time)?
- Which clinical and demographic characteristics, if any, are associated with improvement in exodeviation control and/or treatment success?

1.7 Rationale for Present Study

IXT is a common eye condition, but long-term surgical treatment outcomes are disappointing, with high failure rates due to recurrence or undercorrection of the exodeviation. Patching is a commonly used nonsurgical treatment for which there is some evidence of short-term treatment benefit (improved exodeviation control and reduced angle of deviation) when prescribed 2-3 hours/day. Nevertheless, the extent to which patching is effective if worn for long periods of time per day or if any treatment effect is sustained once treatment is discontinued is unknown.

Understanding the effectiveness of patching treatment and whether there is a benefit from full-time patching versus observation alone has important implications for managing children with IXT. If full-time patching is associated with more improvement in distance control compared to observation alone, then future studies can be conducted to evaluate different durations of full-time patching treatment, whether the effect is maintained off-treatment, and how full-time patching compares to other treatment strategies.

In addition, this study would provide evidence of the ability of patching to alter suppression, anomalous retinal correspondence, and fusional amplitudes, and the relationships of these clinical characteristics with treatment success, failure, and improvement of IXT. This study provides an opportunity to explore such relationships, and data are expected to create hypotheses for future studies.

1.8 Study Objectives

Determine whether full-time patching is more effective than observation for improving distance control of IXT after 3 months of treatment (on-treatment outcome).

1.9 Potential Risks and Benefits of Study Treatment

1.9.1 Known Potential Risks

There is a risk that patching may create diplopia that then becomes troublesome to the patient, but this complication is seldom reported. It is possible that some patients will show worsening of IXT control or increase in magnitude with patching[32] or observation,[22] but deterioration criteria will be assessed after 3 months and the short 3-month duration allows for cessation of patching treatment and/or commencement of other treatment should deterioration of the IXT occur. Skin irritation may occur. If persistent skin irritation occurs due to the adhesive patch, the participant will be provided with a fabric patch to wear on their glasses (plano glasses will be provided for children who are not already wearing glasses). Patching could potentially cause a decrease of VA in the patched eye, but that is very unlikely since alternating patching is prescribed, and any decrease in VA is almost always reversible. One potential risk with observing IXT without treatment is that suppression may increase in density over time. An increase in the density of suppression may predispose the child to worse motor and sensory outcomes in the long term, but with a 3-month study duration there is unlikely to be a significant change, and furthermore this has not been previously studied to know if and when this occurs.

1.9.2 Known Potential Benefits

The potential benefits of patching are improved exodeviation control, reduced angle of deviation, reduced suppression, and/or increased fusional amplitudes.

There are no direct benefits of observation, however, in a previous RCT, approximately 7% of patients[55] resolved spontaneously over 3 years. Therefore, avoiding the need for treatment of IXT and any associated risks of IXT treatment may be considered an indirect benefit of observation.

1.10 Risks of Examination or Testing 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 participant may receive cycloplegic/dilating eye drops.

1.11 Risk Assessment

There are no risks involved in this study that would not be part of usual care when treating with either patching or by observation alone. The protocol's level of risk is consistent with 45 CFR 46.404 and 21 CFR 50.51, which indicates research not involving greater than minimal risk for the individual child involved in the research.

1.12 General Considerations

The study is being conducted in compliance with the policies described in the PEDIG network 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 (GCP).

Chapter 2: Study Enrollment and Randomization

2.1 Participant Recruitment and Enrollment

The study plans to enroll enough participants, for whom informed consent will be obtained, in order to randomize a minimum of 72 participants.

As the randomization goal approaches attainment, sites will be notified of the end date for recruitment into the study. Participants who have signed informed consent forms are enrolled and can be randomized until the end date, which means the expected recruitment number might be exceeded. The maximum number randomized will be 82.

There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. The overall number of participants with an interocular difference in distance VA of 2 logMAR lines (10 letters on E-ETDRS for patients ≥7 years old) will be limited to 14.

2.1.1 Informed Consent

Children with IXT who are 3 to <9 years of age attending ophthalmology or optometry outpatient visits will be identified.

Families who qualify for the study will be approached by one of the research team members. 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 a parent and written or verbal assent from the child (depending on age and local IRB requirements) prior to performing any study-specific procedures that are not part of the child's routine care.

A child is considered enrolled into the study when the informed consent form has been signed by the parent, the assent form has been signed by the child (when applicable), and the investigator has also signed the appropriate forms.

2.2 Eligibility Criteria

2.2.1 Inclusion Criteria

Children under the care of a pediatric optometrist or pediatric ophthalmologist, who are identified during a standard-of-care outpatient visit or from a referral from another provider, will be eligible for the study if they meet all the following criteria:

1. Age 3 to < 9 years
2. IXT meeting all the following criteria:
   - Intermittent or constant XT at distance (mean distance control 2.0 or more) with at least 1 measure of 3, 4 or 5 (i.e., indicating spontaneous tropia) on control testing
   - Either IXT, exophoria, or orthophoria at near (cannot have control score of 5 on all 3 near assessments)
   - Distance exodeviation between 15Δ and 50Δ by PACT
   - Near exodeviation between 0Δ and 50Δ by PACT
   - Near exodeviation does not exceed distance by more than 10Δ by PACT
3. Age-normal visual acuity in both eyes:[56-58]

- 3 years: 20/50 or better (>=63 letters)
- 4 years: 20/40 or better (>=68 letters)
- 5-6 years: 20/32 or better (>=73 letters)
- 7-<9 years: 20/25 or better (>=78 letters)

4. Interocular difference in distance VA of 2 logMAR lines or less (10 letters or less on E-ETDRS for patients ≥7 years old). Testing by ATS HOTV for participants 3 to < 7 years old and by E-ETDRS for participants ≥7 years old.
    - The overall number of participants with an interocular difference in distance VA of 2 logMAR lines (10 letters on E-ETDRS for patients ≥7 years old) will be limited to 14.
5. Refractive error between -6.00 D SE and +2.00 D SE (inclusive) based on cycloplegic refraction performed within 7 months
6. Participants with refractive error meeting any of the following based on cycloplegic refraction performed within the prior 7 months must be wearing spectacles for at least 2 weeks:
    - Myopia > -0.50 D spherical equivalent (SE) in either eye
    - Anisometropia > 1.00 D SE
    - Astigmatism in either eye > 1.00 D
7. Any refractive correction worn at enrollment (required or not) must meet the following guidelines based on cycloplegic refraction performed within the prior 7 months:
    - Anisometropia SE must be within 0.50 D of the full anisometropic difference correction
    - Astigmatism must be corrected within 0.50 D
    - Axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D.
    - For hyperopia, the spherical component can be reduced at investigator discretion provided the reduction is symmetrical and does not meet the definition of deliberate overminus (see below).
    - For refractive errors with an emmetropic or myopic SE, the intent is to fully correct, but the spherical component can be undercorrected at investigator discretion provided the reduction is symmetrical and results in no more than -0.50 D SE residual (i.e., uncorrected) myopia. Deliberate overminus is not allowed.
    - Deliberate overminus is defined for this protocol as any refractive correction prescribed to yield lenses that are overminused by more than -0.50D SE than cycloplegic refraction SE.
        - Less than the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) or no correction for a hyperopic SE refractive error is not considered the same as overminusing for this protocol (because most patients without IXT but with hyperopic SE refractions up to +2.00 D SE would not typically be prescribed a refractive correction.)
    - Note that the refractive correction guidelines and the requirement to wear refractive correction for at least 2 weeks apply not only to participants who require refractive correction under the above criteria but also to any other participant who is wearing refractive correction.
8. Gestational age > 30 weeks

9. Birth weight > 1500 grams
10. Patient and/or parent understands protocol, is willing to enroll, and is willing to accept that other treatment for IXT will not be offered for 3 months
11. Parent has phone and is willing to be contacted by Jaeb Center staff
12. Relocation outside of area of an active PEDIG site within next 3 months not anticipated

2.2.2 Exclusion Criteria

Individuals meeting any of the following criteria at baseline will be excluded from study participation.

1. Prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
2. Prior nonsurgical treatment for IXT (e.g., patching, vergence therapy, vision therapy/orthoptics, base-in prism, or deliberate overminus with spectacles more than 1.00 D) for >1 week duration within the past 1 year
3. Previous amblyopia treatment other than refractive correction
4. Diplopia more than 2 times per day by parental assessment
5. Paretic or restrictive strabismus
6. Craniofacial malformations affecting the orbits
7. Ocular disorders which would reduce VA (except refractive error)
8. Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Participants with mild speech delay or reading and/or learning disabilities or ADHD are not excluded.
9. Neurological anomaly that could affect ocular motility (e.g., cerebral palsy, Down syndrome)
10. Immediate family member (child or sibling) of any investigative site personnel directly affiliated with this study.
11. Known allergy to adhesive patches.
12. Known allergy to silicone.

2.3 Historical Information

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

2.4 Screening and Baseline Procedures

Testing will be done in the order specified below on a single day following enrollment in the child's current refractive correction if worn (any spectacle correction worn must meet the criteria specified in section 2.2) and without cycloplegia:

1. Eye-Related Quality of life: Pediatric Eye Questionnaire (PedEyeQ)
    - Child questionnaire: Completed by children 5 years and older
    - Parent questionnaire: Completed by the parent for all children regardless of age (includes parent and proxy questions)
2. Symptom Survey:
    - Intermittent Exotropia Symptom Survey completed by children 5 years or older.
    - Single diplopia question to be completed by children 3 or 4 years.

3. Diplopia Assessment by Parent: Assess diplopia presence and frequency over the last week, by parental report. If present, classify diplopia frequency as "2 times or less per day" or "more than 2 times per day."
4. Monocular Distance VA Testing: Distance VA testing will be performed by a certified examiner on a certified VA system (EVA or M&S), using the ATS single surround HOTV for participants 3 to <7 years old and using the E-ETDRS for participants ≥ 7 years. The same VA testing method used at enrollment will be used again at 3 months.
5. Stereoacuity Testing: Assessed using the Randot Preschool Stereotest at near (performed at 40 cm) as outlined the *IXT7 Procedures Manual*
6. Control of the Exodeviation #1: Control of the exodeviation at distance (6 meters) then near (1/3 meter) will be assessed using the standardized IXT control scale,[35] as outlined in the *IXT7 Procedures Manual*.
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - The same examiner must assess control for all three assessments of control at each visit.
8. Divergence Amplitude Testing: Measured at distance (6 meters) using the PEDIG-approved prism bar as described in the *IXT7 Procedures Manual*
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - Record the break and recovery points.
9. Convergence Amplitude Testing: Measured at distance (6 meters) using the PEDIG-approved prism bar as described in the *IXT7 Procedures Manual*
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
10. Control of the Exodeviation #2 (repeat) (*see item #7*).
11. Ocular Alignment Testing:
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - Ocular alignment will be assessed by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and near (1/3 meter) as described in the *IXT7 Procedures Manual*.
12. Control of the Exodeviation #3 (repeat) (*see item #7*)
13. Suppression: Assessment of suppression at distance (6 meters) using the Office Suppression Test[59] as described in the *IXT7 Procedures Manual*
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
14. Retinal Correspondence (children 6 to <9 years only): Assessment of retinal correspondence will be made when aligned and also when tropic using the Hering-Bielschowsky After Image Test[60] as described in *the IXT7 Procedures Manual* using the PEDIG-supplied flash unit.
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

2.5 Randomization

Eligible participants will be randomly assigned on the study website to the following treatment:

1. Observation for 3 months – no treatment other than refractive correction
2. Full-time patching (all waking hours) for 3 months (right eye on even days, left eye on odd days), in addition to refractive correction

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

2.5.1 Observation Group

Participants randomized to observation alone will not be allowed to receive any other treatment for IXT, except refractive correction, for 3 months.

2.5.2 Full-Time Patching Group

Participants randomized to the full-time patching group will patch full-time (all waking hours) for 3 months up until the day before the 3-month primary outcome visit. Daily alternate patching will be prescribed (right eye on even days, left eye on odd days). No other treatment for IXT will be used, except for refractive correction.

2.6 Monitoring of Adherence

Site staff will activate and distribute occlusion dose monitors (ODMs) for participants randomized to patching (patching adherence is not applicable to the observation group).

- Adherence with patching will be monitored throughout the study by an ODM worn on the inside of the patch for participants randomized to patching.
- In addition, parents will be asked to record patching wear time and which eye was patched on a study calendar.

Chapter 3: Study Follow-up

3.1 Study Visits

Study follow up for participants randomized in the study is (timed from randomization):

- 4-week phone call: 4 weeks ± 1 week
- 3-month (on treatment) primary outcome visit: 3 months ± 2 weeks
    - Parents will be instructed to not patch on the day of the visit

3.2 Phone Call at 4-weeks

Study personnel will call the parent of each participant 4 weeks ± 1 week following randomization. The purpose of the call for the patching groups is to determine whether patching is being done, and if so, how it is being done. If patching is not being done correctly, patching instructions will be reviewed with the parents. Parents in the patching groups will be asked if they have had any problems using the ODM. If ODMs have been lost, replacement ODMs may be sent to the parent. Parents in both treatment groups will be asked if they have any questions or concerns about the study.

3.3 Masking Procedures

Participants will not be masked to their treatment group, given that they will be asked to patch all waking hours/day (full-time patching group) or not at all (observation group). The investigator treating each participant also will not be masked to treatment group. An examiner masked to treatment group will perform all clinical testing (with the exception of VA testing and administration of questionnaires, which may be performed by unmasked, certified personnel) at the 3-month visit.

3.3.1 Masked Examiner

The masked examiner must be a pediatric optometrist, pediatric ophthalmologist, or certified orthoptist who is not aware of the participant's assigned treatment. Because the enrolling investigator will be unmasked to treatment group, they will not be allowed to serve as their own masked examiner.

3.4 Testing Procedures at 3-Month Outcome Visit

The following procedures will be performed in the order specified below at the 3-month outcome visit with the participant wearing their current refractive correction (if worn), and without cycloplegia. If unable to complete the entire masked exam during the office visit, the participant can return with 10 days to complete all masked testing (# 6-14 below). Testing procedures #1-5 below do not need to be repeated if completed at the initial office visit.

1. Adherence Monitoring (for patching group):
    - Evaluate compliance by review of study calendar
    - Download adherence data from ODM
2. Eye-Related Quality of life: Pediatric Eye Questionnaire (PedEyeQ)
    - Child questionnaire: Completed by children 5 years and older
    - Parent questionnaire: Completed by the parent for all children regardless of age (includes parent and proxy questions)
3. Symptom Survey:

- Intermittent Exotropia Symptom Survey completed by children 5 years or older.
- Single diplopia question to be completed by children 3 or 4 years.

4. Diplopia Assessment by Parent: Assess diplopia presence and frequency over the last week, by parental report. If present, classify diplopia frequency as "2 times or less per day" or "more than 2 times per day."
5. Monocular Distance VA Testing: Distance VA testing in each eye using the same test method used at enrollment.
6. Stereoacuity Testing **(masked):** Randot Preschool Stereoacuity at 40 cm.
7. Control of the Exodeviation #1 **(masked):**
   - Distance (6 meters)
   - Near (1/3 meter)
   - The same examiner must assess control for all three assessments of control for each visit.
8. Divergence Amplitude Testing **(masked):** Measured at distance (6 meters) using a PEDIG-approved prism bar as described in the *IXT7 Procedures Manual*
   - Record the break and recovery points
9. Convergence Amplitude Testing **(masked):** Measured at distance (6 meters) using a PEDIG-approved prism bar as described in the *IXT7 Procedures Manual*
   - Record the blur, break, and recovery points
10. Control of the Exodeviation #2 **(masked)** (repeat) (see item #7)
11. Ocular Alignment Testing (**masked**):
    - Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
    - Ocular alignment will be assessed by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and near (1/3 meter) as described in the *IXT7 Procedures Manual*.
12. Control of the Exodeviation #3 **(masked)** (repeat) (see item #7)
13. Suppression **(masked):** Assessment at distance using the Office Suppression Test at distance (6 meters) as described in the *IXT7 Procedures Manual*
14. Retinal correspondence **(masked):** In children aged 6, 7, or 8 years of age at randomization, assessment of retinal correspondence will be made using the Hering-Bielschowsky After-Image Test as described in *the IXT7 Procedures Manual* using the PEDIG-supplied flash unit.

3.5 IXT Treatment Changes During Follow-up

Changes in treatment are not allowed prior to the 3-month outcome visit.

If the participant is experiencing overwhelming social concerns or significant symptoms associated specifically with IXT, the investigator **must call one of the Protocol Chairs** to discuss the case and obtain approval for an early 3-month outcome visit (if not already in window) prior to initiating any non-randomized treatment for IXT.

3.6 Management of Refractive Error During Follow-up

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 3-month outcome visit, the spectacles may only be replaced with the same spectacle prescription that was prescribed at randomization.

Chapter 4: Testing Procedures and Questionnaires

4.1 Clinical Assessments

The following test procedures will be completed for all three treatment groups at each visit as defined in the *IXT Procedures Manual:*

1. Monocular VA Testing: Distance VA will be tested in both eyes with the participant wearing their study-specified spectacle correction. The right eye is tested, with the left eye occluded with an adhesive patch. The left eye is tested after the right eye. Testing must be performed by a certified examiner on a certified VA system (EVA or M&S), using the ATS single surround HOTV for participants 3 to <7 years old and using the E-ETDRS for participants ≥ 7 years. The same testing method must be used throughout the study. Testing time for both eyes typically is in the range of 5 to 10 minutes.

2. Randot Preschool Stereoacuity Test: The Randot Preschool Stereoacuity Test measures 6 levels (40 to 800 seconds of arc) of stereoacuity at near (40 cm). The test consists of 3 booklets, each designed to test 2 levels of stereoacuity, and each level consisting of 4 panels, 3 of which contain a random dot stereogram. The participant wears polarized lenses over their spectacle correction. The examiner asks the participant if they can identify a specific black and white shape in the booklet and then asks the participant to point to the panel containing the corresponding stereogram image, as outlined in the *IXT7 Procedures Manual*. The test must be administered by a certified examiner. The certified examiner will be required to be masked to treatment group. Testing time is approximately 2-4 minutes.

3. Ocular Alignment: Ocular alignment will be assessed by the cover/uncover test, simultaneous prism and cover test when tropia present by cover/uncover test (SPCT), and prism and alternate cover test (PACT), using the PEDIG-approved IXT7 prism bar, in primary gaze at distance (6 meters) and at near (33 cm) as outlined in the *IXT7 Procedures Manual*. The examiner will be required to be masked to treatment group. Testing time is approximately 2-4 minutes.

4. Cycloplegic Refraction: A cycloplegic refraction will be done prior to enrollment and only if clinically indicated thereafter. After administration of eye drops, it typically takes 30 minutes to achieve cycloplegia, and testing time for refraction of both eyes is in the range of 2 to 10 minutes.

5. Suppression Testing: Suppression will be assessed using the Office Suppression Test which grades the level of suppression while tropic on a 4-level scale. Testing will be performed at 6 meters as outlined in the *IXT7 Procedures Manual*. Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist. The examiner will be required to be masked to treatment group. Testing time is approximately 3-5 minutes.

6. Retinal Correspondence Testing: In children 6, 7, or 8 years old at time of randomization, retinal correspondence status will be assessed by the Hering-Bielschowky after-image test, using a PEDIG-provided flash unit. Correspondence will be assessed when aligned and when tropic to record overall status as either:

Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist as outlined in the *IXT7 Procedures Manual*. The examiner will be required to be masked to treatment group. Testing time is approximately 3-5 minutes.

7. Control of IXT: Assessment of IXT control will be performed using the Office Control Scale[35] at both distance (6 meters) and near (1/3 meter), fixating an accommodative target. Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist as outlined in the *IXT7 Procedures Manual*. The examiner will be required to be masked to treatment group. Testing time is approximately 3-5 minutes.
   The scale below applies to both distance and near test distance 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 (in seconds) it takes for the reestablishment 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-uncover test but an exodeviation by PACT, the control scale applies to the exodeviation.

8. Measurement of Divergence Amplitude: Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist. The examiner will be required to be masked to treatment group. Testing time is approximately 2-4 minutes.
    - Divergence amplitude to be measured at distance (6 meters)
    - Using the PEDIG-approved IXT7 prism bar, record the break, and recovery points according to the *IXT7 Testing Procedures Manual.*
    - If manifest exotropia is present at the time of testing, amplitude testing will be recorded as "unable."

9. Measurement of Convergence Amplitudes: Testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist. The examiner will be required to be masked to treatment group. Testing time is approximately 2-4 minutes.
    - Convergence amplitude to be measured at distance (6 meters)
    - Using the PEDIG-approved IXT7 prism bar, record the blur, break, and recovery points according to the *IXT7 Testing Procedures Manual.*
    - If manifest exotropia is present at the time of testing, amplitude testing will be recorded as "unable."

The following information will be collected by interviewing the parent(s) or reviewing the medical record:

1) Date of birth, sex, race, ethnicity, spectacle correction, and prior treatment for IXT. Assessment of Adverse Events: All adverse events including ocular adverse events, and any events judged by the investigator to be related to patching treatment, occurring between the time of initiating study eye treatment and the 12-month outcome exam will be recorded.

Each questionnaire is described briefly below. The procedures for administration are described in the *IXT7 Testing Procedures Manual*.

1. Pediatric Eye Questionnaire (PedEyeQ)[61]

The Pediatric Eye Questionnaire (PedEyeQ), is a pediatric eye-related quality of life and functional vision instrument, validated for use in children with a variety of pediatric eye conditions. The PedEyeQ is patient- and parent-derived and consists of age-appropriate Child and Proxy components as well as a Parent component (to assess the effect on the parent themselves).

i. The Child PedEyeQ, designed for children 5 to 17 years, has the following 4 domains: Functional Vision, Bothered by Eyes and Vision. Social, and Frustration / Worry.

ii. The Proxy PedEyeQ, designed for parents of children 0 to 17 years, has the following 5 domains: Functional Vision, Bothered by Eyes and Vision, Social, Frustration / Worry, and Eye care. Both the Child and Proxy PedEyeQ assess the eye-related quality of life and functional vision of the child.

iii. The Parent PedEyeQ addresses the effect of the child's eye condition on the parent and has the following 4 domains: Impact on Parent and Family, Worry about Child's Eye Condition. Worry about Self-perception and Interactions, and Worry about Functional Vision.

Each of the Child, Proxy, and Parent domains is independently scored using established Rasch look-up tables and converted on a scale of 1 to 100 (each domain scored separately for each instrument). Completion time is approximately 10 minutes for the child, 10-15 minutes for the parent; child and parent questionnaires can be completed concurrently. The PedEyeQ questionnaires administered at enrollment will be the versions repeated throughout the study.

2. Intermittent Exotropia Symptom Survey[62]

The Intermittent Exotropia Symptom Survey is a patient- and parent-derived intermittent exotropia-related symptom instrument designed to identify the presence and severity of symptoms in children with IXT. This questionnaire consists of 22 items completed by children aged 5 years or older.

- All children will use the three-level response scale (not at all, sometimes, a lot), administered by clinical staff either verbally or using a matching card.
- 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 at enrollment will not complete the full questionnaire, but will answer the single question (#8) regarding diplopia. Time for completion of the full Symptom Survey is 5-7 minutes.

3. ***Assessment of Diplopia by Parent***

An estimate of the frequency of diplopia (if any) will be determined by asking the parent whether "your child has complained of double vision over the last week." If yes, the parent is asked how frequently the child has complained of double vision: "2 times or less per day," "or "more than 2 times per day." Any study personnel may ask the parent to rate diplopia. Testing time is approximately 1 minute.

Chapter 5: Unanticipated Problem and Adverse Event Reporting

5.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Sites must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting.

5.2 Adverse Events

Although no adverse events are anticipated, any new reduction in VA of 3 or more lines (≥15 letters on ETDRS) or reduction in Randot Preschool Stereoacuity of 2 or more levels, will be tabulated between treatment groups.

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.

5.3 Safety Oversight

A Data and Safety Monitoring Committee (DSMC) will review compiled safety data at periodic intervals, with a frequency of no less than twice a year. The DSMC can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMC review will be documented in a separate DSMC charter.

The objective of the DSMC review is to decide whether the study (or study treatment for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site, or for the entire study) is a potential outcome of a DSMC safety review.

5.4 Stopping Criteria

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of follow-up for all study participants. There are no pre-specified formal guidelines for stopping the study for futility or efficacy.

5.5 Participant Discontinuation of Study Treatment

Rules for discontinuing study treatment use are described below.

- The investigator believes it is unsafe for the participant to continue to receive the treatment.
- The participant or parent requests that the treatment be stopped.

Even if the study treatment is discontinued, the participant will be encouraged to remain in the study through the 3-month visit.

Chapter 6: Miscellaneous Considerations

6.1 Contacts by the Jaeb Center for Health Research and Sites

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

6.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

6.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

6.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

Chapter 7: Statistical Considerations

7.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

7.2 Primary Objective and Hypothesis

The study has one primary objective:

1) To determine if participants with IXT undergoing full-time patching have more improvement in mean distance control between baseline and 3 months than participants being observed without treatment.

The primary outcome is a comparison of the change in the mean distance control scores (average of 3 measurements) at 3 months between the full-time patching group and the observation group.

The study is designed as a superiority study to evaluate two 2-sided primary null hypotheses that the changes in the mean control scores in the two groups at 3 months are the same versus the alternative hypothesis that they are different.

Hypothesis Test for Objective # 1 – FT vs OBS at 3 Months:

$\mathbf{H_{null}}$ $\quad FT_{\text{mean change in distance control over 3 months}} = OBS_{\text{mean change in distance control over 3 months}}$

$\mathbf{H_{alternative}}$ $\quad FT_{\text{mean change in distance control over 3 months}} \neq OBS_{\text{mean change in distance control over 3 months}}$

7.3 Sample Size

Sample size estimation is based on data from our previous IXT2 randomized trial comparing observation versus part-time patching for intermittent exotropia, limited to 278 participants with similar baseline age (3 to <9 years) and baseline control score at distance (2 or higher).[22] Data are summarized in Table 1 below.

Table 1 – Previous IXT2 Randomized Trial Data in 3- to <9-Year-Olds with IXT*

Distance Control Scores**	Cohort	
	IXT2 Glasses Alone (Observation)	IXT2 Part-time Patching (3 hours/Day)
Baseline		
n	147	131
Mean (SD)	2.88 (1.01)	2.93 (1.00)
3-Month Score		
n	131	116
Mean Score (SD)	2.59 (1.35)	2.15 (1.23)
95% CI for Mean Score	2.35 to 2.82	1.92 to 2.37
95% CI for SD Score	1.21 to 1.54	1.09 to 1.41
3-Month Change from Baseline		
n	131	116
Mean Change (SD)	0.30 (1.23)	0.78 (1.38)
95% CI for Mean Change	0.09 to 0.51	0.53 to 1.04
95% CI for SD Change	1.09 to 1.40	1.22 to 1.59

*Participants aged 3 to <9 years old with baseline distance control score of 2 or higher (worse).
** A single measure of control was obtained at each visit in the IXT2 study.

In IXT2, after 3 months of observation versus treatment with 3 hours per day patching, the observation group had a mean change based upon a single measure of distance control of 0.30 points (95% CI, 0.09 to 0.51 points) with a standard deviation of 1.23 points (95% CI, 1.09 to 1.40 points); and the 3 hours per day patching group had a mean change based upon a single measure of distance control of 0.78 points (95% CI, 0.53 to 1.04 points) with a standard deviation of 1.38 points (95% CI, 1.22 to 1.59 points); group difference patching – observation = 0.49 (95% CI 0.16 to 0.81). The correlation between distance control score at baseline and change from baseline after 3 months was R=0.39 (95% CI, 0.27 to 0.48).

We are aware of no previous data on distance control score among children with IXT treated with full-time patching. In our IXT5 study, after 6 months of treatment with overminus spectacles, the mean change in distance control was 1.40 points (95% CI, 1.18 to 1.63 points) with a standard deviation of 1.48 points (95% CI, 1.34 to 1.66 points). There was no 3-month outcome in the IXT5 study; however, in the IXT3 pilot study, those treated with overminus spectacles improved on average 1.2 points (95% CI, 0.5 to 1.9 points) with a standard deviation of 1.8 points (95% CI, 1.4 to 2.5 points) after 8 weeks. Therefore, we estimate that a mean change of 1.45 points after 3 months of full-time patching in the current study is reasonable for an active treatment.

Sample Size Estimation:

The study will be powered for the primary objective.

Assuming a mean change in distance control score after 3 months of 0.30 points in the observation group and 1.45 points in the full-time patching group; we estimate that the true difference is 1.15 points between full-time patching and observation at 3 months.

Hypothesis Test for Objective – FT vs OBS at 3 Months:
Assuming a pooled standard deviation of 1.5 points for change in distance control score after 3 months, and a correlation of 0.30 between distance control score at baseline and change from baseline after 3 months, a total sample size of 68 participants (34 per group) completing the 3-month outcome has 90% power with a type I error rate of 5% to evaluate whether there is a treatment group difference between FT patching and OBS if the true difference is 1.15 points, Table 2. Accounting for 5% loss to follow-up after 3 months, a total of 72 participants (36 per treatment group) will need to be enrolled. The overall number of participants with an interocular difference in distance VA of 2 logMAR lines (10 letters on E-ETDRS for patients ≥7 years old) will be limited to 14.

Table 2: Total Sample Size for Difference in Mean Distance Control Score

Standard Deviation of Change in Distance Control (points)	Treatment Group Difference for Outcome of Mean Change in Distance Control (points)		
	0.85	**1.00**	**1.15**
1.4	106	78	60
1.5	122	90	68
1.6	138	100	78

Cells indicate N for the overall study (two treatment groups combined with a ratio of 1:1), using a 2-sided test with alpha 0.05, from an analysis of covariance model evaluating a difference between treatment groups for mean change from baseline in distance control, controlling for baseline distance control.

If the true effect with FT patching is as small as 0.99, the study would still have 80% power to reject the null in favor of a difference (and 1.05 with 85%).

7.4 Interim Monitoring
Given the short duration of the primary outcome at 3 months, there will be no formal interim analysis for stopping the study early for efficacy or futility.

7.5 Analysis Datasets
The primary efficacy analysis will follow an intent-to-treat (ITT) principle. Therefore, the primary analysis dataset will include all randomized participants with imputation for those missing the 3-month outcome and will analyze them according to the group they were originally assigned. Sensitivity analyses of the primary outcome will follow a modified ITT principle and use observed data with no imputation for missing outcomes.

7.6 Analysis of the Primary Efficacy Endpoints
The mean of three individual distance control scores will be tabulated by treatment group at 3 months. The change from baseline in mean control score (mean of three assessments) will be compared between the FT patching group and the OBS group at 3 months using an analysis of covariance (ANCOVA) model that adjusts for the mean distance control score at baseline and distance angle by PACT at baseline. An estimate of difference between the groups will be reported along with a 95% confidence interval and p-value.

When the protocol-specified three measures of control are not performed at the outcome exam, the mean of two tests will be used for analysis if only 2 distance control tests are completed; the single distance control score will be used for analysis if only 1 testing is completed.

Participants who miss the 3-month visit or who do not complete any control testing at the 3-month visit will have an average distance control score imputed using multiple imputation.

The multiple imputation will be performed using Monte Carlo Markov Chain (MCMC) modeling that includes the mean distance controls at the outcome visit and the following baseline factors: mean distance control, and distance PACT.

7.6.1 Sensitivity Analyses

The following analyses will be performed as sensitivity analyses to the primary analysis:

Sensitivity Analysis #1 (Complete Case Analysis Including Visits within Analysis Window):

- All participants who complete 1 or more distance control tests at the 3-month visit within the analysis window (± 1 month) will have their observed 3-month data analyzed
- Participants who miss the 3-month visit entirely or who do not complete any control testing at the 3-month visit within the analysis window will be excluded from the analysis

Sensitivity Analysis #2 (Complete Case Analysis Including Visits within Protocol Window):

- Repeat the above sensitivity analysis using observed data from participants who completed the 3-month visit within the protocol window (± 2 weeks).

Sensitivity Analysis #3 (ITT minus participants with IOD 2 logMAR lines at enrollment):

- The overall number of participants with an interocular difference in distance VA of 2 logMAR lines (10 letters on E-ETDRS for patients ≥7 years old) will be limited to 14.
- The ITT analyses as described in 7.5 will be repeated excluding these participants.

7.7 Analysis of the Secondary Endpoints

All secondary analyses described below will use observed data only. Treatment group comparisons specified in the sections below will be controlled using false discovery rate (FDR) at the 5% probability level to account for the multiple outcomes. For all secondary analyses, an estimate of difference between the groups will be reported at each timepoint along with an FDR-adjusted confidence interval and p-value unless otherwise specified. Further details about the secondary analyses below will be part of a separate statistical analysis plan (SAP).

7.7.1 Near Control

At 3 months, near control will be evaluated similarly to the distance control primary analysis (section 7.6) using ANCOVA models that adjust for the mean near control score at baseline and the near angle by PACT at baseline.

Additionally, the proportion of participants with 2 or more points improvement in control from baseline will be compared between the treatment groups at 3 months using a two-sided Barnard's test with calculation of a two-sided FDR-adjusted confidence interval on the difference in proportions. This will be done separately for control at distance and near.

7.7.2 Angle of Deviation

At 3 months, a two-sided comparison of magnitude of the angle of deviation by PACT will be performed between treatment groups using an ANCOVA model, which adjusts for baseline PACT. The treatment group difference and an FDR-adjusted confidence interval will be calculated. The analysis will be completed separately at distance and at near.

Additionally, the proportion of participants with improvement of distance and near angle greater than the test/retest variability[63] will be compared between the treatment groups at 3 months using a two-sided Barnard's test with calculation of a two-sided FDR-adjusted confidence interval on the difference in proportions.

7.7.3 Level of Suppression

The proportion with each level of suppression (negligible, mild, moderate, or dense) will be compared between treatment groups at 3 months using an exact Wilcoxon rank sum test.

7.7.4 Proportion with Anomalous Retinal Correspondence

For those able to perform the test, the proportions of normal versus anomalous retinal correspondence will be compared between treatment groups at 3 months using a two-sided Barnard's test for the difference in proportions.

7.7.5 Convergence and Divergence Fusional Amplitudes

The distribution of fusional convergence amplitude (blur point, break point, and recovery) and fusional divergence amplitude (break point and recovery point) will be described and compared between treatment groups at 3 months using an exact Wilcoxon rank sum test. When no blur is reported for fusion convergence, the break point will be used for analysis.

7.7.6 IXT Symptom Survey Score

The IXT Symptom Survey will be completed by children at the enrollment and 3-month exams. The distribution for each individual item ('Never', 'Sometimes', 'All the Time) will be tabulated for each treatment group within subgroups defined by age 5 to 9 years (all items) and age <5 years for the single diplopia question.

7.7.7 PedEyeQ Score

The PedEyeQ consists of 3 components: child, proxy, and parent. After applying existing Rasch scoring,[61] the average score for each of the domains within the three components will be compared between treatment groups at 3 months using an ANCOVA model, which adjusts for baseline PedEyeQ score. The treatment group difference and an FDR-adjusted confidence interval will be calculated.

7.7.8 Binocular Diplopia by Parental Report

The proportion of binocular diplopia at 3 months with a frequency of "more than 2 times per day" over the last week at distance or near, by parental report will be compared treatment groups at 3 months using a two-sided Barnard's test.

7.8 Exploratory Analyses

Exploratory analyses described below will use observed data only. Point estimates and 95% CIs will be reported for each outcome with no adjustment for multiplicity.

7.8.1 Actual Patch Wear Time

The distribution of actual patch wear time will be tabulated overall and by treatment groups. The potential correlation between actual patch wear time in the FT patching group and the change from baseline in the following outcomes will be evaluated at 3 months (when collected):

1. Distance control score
2. Near control score
3. Distance angle of deviation
4. Near angle of deviation
5. Level of suppression
6. Convergence fusional amplitudes
7. Divergence fusional amplitudes
8. Symptom survey score
9. Diplopia assessment by Parent
10. PedEyeQ score (each domain)

A Spearman correlation coefficient and 95% confidence interval will be calculated for each outcome.

7.8.2 Outcome of Retinal Correspondence Testing

The relationship of retinal correspondence response with respect to the following outcomes within each treatment group will be evaluated at 3 months:

1. Distance control score
2. Near control score
3. Distance angle of deviation
4. Near angle of deviation
5. Level of suppression
6. Convergence fusional amplitudes
7. Divergence fusional amplitudes
8. Symptom survey score
9. Diplopia assessment by Parent
10. PedEyeQ score

For continuous outcome variables, the difference in means between participants with normal versus anomalous retinal correspondence will be calculated along with a 95% confidence interval. For categorical outcome variables, the difference in proportions between participants with normal versus anomalous retinal correspondence will be calculated along with a 95% confidence interval.

7.8.3 Subgroup Analysis of Distance Control

The treatment group comparison of distance control will be assessed at 3 months in subgroups based on gender and race/ethnicity in accordance with NIH guidelines; however, no effect modification is expected for these factors.

7.9 Safety Analyses

7.9.1 Deterioration

The number and proportion of participants with deterioration, as defined below, will be tabulated for each treatment group at 3 months as a safety outcome.

Deterioration is defined as meeting one of the following criteria at the 3 months follow-up visit:

1. Constant exotropia at least 10Δ at distance **AND** near by SPCT:
    - Constant is defined as an exotropia present throughout the examination and confirmed by cover/uncover testing performed at least 3 different times over the course of the exam (including during assessment of IXT control).
2. Decrease in near stereoacuity of at least 2 levels from baseline, or to nil, measured using the Randot Preschool Stereotest.

7.9.2 Reduction of Distance Visual Acuity

Any cases of 1) interocular difference ≥0.3 logMAR and 2) reduced visual acuity in best refractive correction (≥0.3 logMAR) in either eye will be tabulated by treatment group at 3 months.

7.9.3 Diplopia

After 3 months, any new cases of diplopia 'Sometimes' or 'All the Time', based on response to item 8 from the IXT symptom survey (asked as a single question for children ages 3 and 4 years of age) will be tabulated for each treatment group. In addition, diplopia occurring 'Never', 'Sometimes', or 'All the Time' will also be tabulated for each treatment group.

7.10 Patching Adherence

Patching adherence (as reported by the parent) will be tabulated at the 3-month visit for the FT patching treatment group, as will reasons for any major deviations.

7.11 Additional Tabulations and Analyses

The following tabulations and analyses will be performed:

- A flow chart accounting for all participants according to treatment group
- Visit completion rates according to treatment group
- Baseline demographics and clinical characteristics overall and by treatment group at randomization
- Protocol deviations according to treatment group

Chapter 8: Data Collection and Monitoring

8.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live participant must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

8.2 Study Records Retention

Study documents should be retained for a minimum of 3 years after completion of the final grant reporting. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

8.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol adhering to Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data.

Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

8.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 9: Ethics/Protection of Human Participants

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

9.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 Informed Consent Process

9.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records

(office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Jaeb Center for Health Research staff will be secured and password protected.

At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

9.3.3 Future Use of Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made available to the public.

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