INTERMITTENT EXOTROPIA STUDY 1 (IXT1)

A Randomized Trial of Bilateral Lateral Rectus Recession versus Unilateral Lateral Rectus Recession with Medial Rectus Resection for Intermittent Exotropia

PROTOCOL

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PROTOCOL AMENDMENT IV (6-21-17)

This amendment applies to subjects participating in the optional extension study from >3 years to 8 years after randomization, which is described in Protocol Amendment II.

Protocol Change #1

Current Protocol (Protocol Amendment III 6-18-15)
Symptoms of diplopia are not assessed in the current version of the protocol.

Proposed Change
To assess symptoms of diplopia by asking subjects to complete the Diplopia Questionnaire at the 8-year visit.

Rationale for Change
Diplopia (double vision) is an important long-term outcome following surgery for strabismus and may be an adverse effect of either or both the surgical approaches used in the study. We proposed to collect standardized data to determine the frequency of this potential adverse effect and whether it differs between treatment groups. The Diplopia Questionnaire[1] is a validated, reliable 8-item self-administered questionnaire designed to assess the presence and frequency of diplopia in specific gaze positions.

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PROTOCOL AMENDMENT III (6-18-15)

This amendment applies to subjects participating in the optional extension study described in Protocol Amendment II.

Protocol Change #1

Current Protocol (Protocol Amendment II 2-10-15)

In the additional 5 years of follow up provided for by Protocol Amendment II (>3 years to 8 years after randomization), the study will cover the costs of each annual visit because they include testing procedures that are not standard care in all practices. Any other visits that are part of routine care will be the subject's (or his/her insurance companies) responsibility.

Proposed Change

In the additional 5 years of follow up provided for by Protocol Amendment II (>3 years to 8 years after randomization), the study will pay for visits specific to the research study, but will not pay for usual care visits that would occur whether or not the child was in the study. The cost of usual care visits will be the parent(s) or their insurance company's responsibility.

Rationale for Change

Some visits will be needed as part of normal care; while some will be research related. The investigator will determine whether each annual visit is considered routine patient care or specific to the research study.

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PROTOCOL AMENDMENT II (2-10-15)

This optional amendment provides for study subjects to have an additional five years of follow up after the 3-year primary outcome (>3 years to 8 years from randomization).

Objective

To compare long-term outcomes between subjects originally treated with bilateral lateral rectus muscle recession versus unilateral lateral rectus recession with medial rectus resection for the treatment of basic type and pseudo divergence excess type intermittent exotropia.

Protocol Specified Follow-up Visits

Visits will occur at 4, 5, 6, 7, and 8 years (±2 months) from randomization. Additional follow-up visits are at investigator discretion.

Study Procedures and Data Collection

The following testing procedures will be performed in the following order:*

1. Health-Related Quality of Life Questionnaire *(8-year visit only)*
2. Diplopia Questionnaire *(8-year visit only)*
3. Visual acuity
    - Testing will be performed using the electronic E-ETDRS testing protocol
    - Testing must be performed in current refractive correction, if worn.
        - If prism is currently prescribed, visual acuity testing should be performed *with* prism.
        - If deliberate overminus** is currently prescribed, visual acuity testing should be performed *with* the overminus correction.
    - If visual acuity is 20/32 or worse (75 letters or less) in either eye, a manifest refraction must be performed. If the examiner believes that the patient's current correction is not optimal, trial frames with new correction should be used for all testing at the visit. This includes testing visual acuity again, with the patient wearing trial frames.
4. Control of exodeviation assessment at distance and near #1:
    - Testing must be performed in current refractive correction.
        - If prism is currently prescribed, testing should be performed *without* prism.
        - If deliberate overminus** is currently prescribed, testing should be performed in trial frames *without* the overminus component of the prescription.
5. Preschool Randot stereoacuity testing at near (performed at 40 cm)
    - Testing must be performed in current refractive correction.
        - If prism is currently prescribed, stereoacuity testing should be performed *with* prism.
        - If deliberate overminus** is currently prescribed, stereoacuity testing should be performed *with* the overminus correction.
    - Stereoacuity is tested immediately following the first assessment of control of the exodeviation; no 10-minute break is needed.
6. Ocular alignment testing in prism or deliberate overminus *(for patients currently prescribed prism or deliberate overminus)*

- Measure ocular alignment at near only, in the primary position using cover/uncover, SPCT and PACT
- This testing should be performed *with* prism or deliberate overminus (as applicable).

7. Control of exodeviation assessment at distance and near #2 (repeat) (*see item #2*)
   - The second control testing is performed immediately after the previous testing—it does not need to be performed before dissociative testing and no 10-minute break is needed.
   - The same examiner should assess IXT control each of the three different times that control is assessed during the annual study visit.
8. Ocular alignment in the primary position using cover/uncover, SPCT and PACT at distance and near
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, ocular alignment testing should be performed *without* prism.
     - If deliberate overminus** is currently prescribed, ocular alignment testing should be performed in trial frames *without* the overminus component of the prescription.
9. Control of exodeviation assessment at distance and near #3 (repeat) (*see item #2*)
   - The third control testing is to be performed immediately after the previous testing—it does not need to be performed before dissociative testing and no 10-minute break is needed.
   - The same examiner should assess IXT control each of the three different times that control is assessed during the annual study visit.
10. Cycloplegic refraction *(7-year visit only)*
    - If the current correction at the 7-year visit is not optimal based on the cycloplegic refraction, new spectacles should be prescribed.

*Testing procedures are performed as described in section 2.5 *unless otherwise specified above*.

**Deliberate overminus lenses = lenses that yield > 0.50 D *more minus* spherical equivalent (SE) than the refraction SE.

All testing procedures are assessed unmasked.

At each annual visit, data on treatments used or prescribed, current refractive correction, and the last refraction will be recorded.

Treatment

Treatment in the extension study is at investigator discretion, including non-surgical treatment and reoperation.

Costs

The parent/guardian of each subject will be compensated $50 per visit for completion of each annual protocol-specified follow-up visit (4-, 5-, 6-, 7-, and 8- year) for a maximum of $250. If there are extenuating circumstances, and the subject is unable to complete the annual study visits without additional funds due to travel costs, additional funds may be provided.

In the additional 5 years of follow up provided for by Protocol Amendment II (>3 years to 8 years after randomization), the study will pay for visits specific to the research study, but will not

pay for usual care visits that would occur whether or not the child was in the study. The cost of usual care visits will be the parent(s) or their insurance company's responsibility.

Treatment is at investigator discretion and is not part of this protocol. Any costs associated with treatment will not be paid for by the study. The study will pay for a pair of spectacles (lenses and frames) at the 7-year visit; spectacle changes / new spectacles prescribed at other times will not be paid for by the study.

Risks

The procedures in this study are part of daily eye care practice in the United States and pose no known risks.

Subject Contact During Follow Up

Between annual visits, subjects will be called by the Jaeb Center to promote retention; birthday and holiday cards will be sent annually, and a subject newsletter may be sent.

Re-consenting of Subjects

An informed consent form for the extension study will be signed by parents who elect to continue their child's study participation. An assent for the extension study will be signed by the participating subject, as applicable. Re-consenting generally will occur at the 3-year visit but could occur at other times either before or after participation in the 3-year study has ended. A subject (and respective parent) may withdraw from the study at any time.

Statistical Analysis

Statistical analyses will primarily be cross-sectional comparisons of outcomes including ocular alignment, exotropia control, and stereoacuity between treatment groups at each annual visit.

The analysis of the primary basic IXT cohort will be considered primary whereas the analyses in the smaller primary pseudo divergence excess IXT cohort and the secondary cohort will be considered exploratory.

Statistical analyses may also be performed combining some or all of the cohorts.

A detailed statistical analysis plan will be written and finalized prior to the completion of the study and may supersede the plan briefly described herein.

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PROTOCOL AMENDMENT (4-30-10)

This amendment provides for the following protocol changes:

Protocol Change #1

Current Protocol
One of the eligibility criteria requires the largest exodeviation at either distance or near to be between 15 and 50 PD (inclusive) by prism and alternate cover test (PACT).

Proposed Change
Change the eligibility criteria to require that the largest exodeviation at either distance, near, *or remote distance* be between 15 and 50 PD (inclusive) by prism and alternate cover test (PACT) (sections 1.3, 1.4, 2.2.1, and 6.1). Add an additional eligibility criterion requiring that the exodeviaton must be at least 15 PD at distance or near (sections 1.3, 1.4, and 2.2.1).

Rationale for Change
Surgical dose must be based on the largest angle uncovered by PACT at distance (6 meter), near, or remote distance (at least 50 feet). The largest angle in the surgical dose tables in the protocol is 50 PD because BLRrec is considered by many clinicians to be inadequate for correcting angles larger than 50 PD. Because randomization would not be appropriate for patients with angles greater than 50 PD, the eligibility criteria is being tightened to exclude not only patients with distance or near angles >50 PD, but also those patients with remote distance angles >50 PD.

Because one of the criteria for surgical success at 3 years requires a reduction of more than 10PD in the largest of the distance and near angles at enrollment, the additional eligibility criteria requiring that the angle be at least 15 PD at distance or near was needed to ensure that more than 10 PD improvement would be possible in at least the distance or the near angles.

Protocol Change #2

Current Protocol
There is no upper limit on the amount of hyperopia allowed for eligibility. Refractive correction is required for patients with hyperopia >+5.00 D and the guidelines for prescribing refractive correction specify that residual (uncorrected) hyperopia cannot exceed +5.00 D.

Proposed Change
Add an eligibility criterion which specifies ‘no hyperopia greater than +3.50 D spherical equivalent (SE) in either eye’ (sections 1.3, 1.4, and 2.2.1). Omit from the enrollment chapter the guideline requiring spectacle correction be prescribed for hyperopia >+5.00 D and the guideline requiring that spectacle correction have no more than +5.00 D residual hyperopia (section 2.2.1). For follow up, change to require refractive correction for patients with hyperopia >+3.50D (section5.3.1) and change refractive correction guidelines to specify that residual (uncorrected) hyperopia cannot exceed +3.50 D (section5.3.2).

Rationale for Change

The proposed changes are to make refractive error eligibility and prescription guidelines consistent with those in the IXT2 study. The reasons for this change are as follows: 1) it was felt that making these items parallel between the two studies will avoid confusion among study investigators, 2) it is expected that the percentage of otherwise-eligible IXT patients with hyperopia greater than +3.50 D SE is very low, and 3) that patients with very high hyperopia might be more likely to have a neurologic condition and might be a different than the typical IXT patient

Protocol Change #3

Current Protocol

All patients are randomized regardless of whether the magnitude of their exodeviation increased or decreased out of study eligibility range (15 to 50 PD) before surgery has occurred.

Proposed Change

Patients in whom the magnitude of the largest of the most recent distance, near, and remote distance angles has decreased to <15 PD or increased to >50 PD before surgery will be dropped from the study if they have not yet been randomized. If such patients have already been randomized, it is at investigator discretion whether to perform surgery and what type of surgical method to perform (i.e. BLRrec, R&R, or any other type of procedure). Changes made to sections 2.6 and 3.1.

Rationale for Change

The study is aiming to evaluate surgical outcomes in patients whose largest preoperative angle is between 15 and 50 PD. Given that the surgery window extends to 60 days after enrollment and that surgery could potentially occur even later, it is possible that a patient's exotropia could increase or decrease out of the eligibility range of 15 to 50 PD before surgery. As discussed in protocol change #1 above, randomization to BLRrec or R&R would not be appropriate in patients whose angle was greater than 50 PD. In addition, the largest preoperative angle is required to be a minimum of 15 PD to ensure that a reasonable amount improvement would be required to meet one of the study's treatment success criteria--an exodeviation less than 10 PD by PACT at distance and near and reduction of more than 10 PD from largest of distance and near angles at enrollment.

Protocol Change #4

Current Protocol

Currently the surgical dose tables start with doses for 15 PD angles.

Proposed Change

In surgical dose tables 1 and 2 (section 3.3), removed 15 PD angles, added 16 PD angles using the 15 PD doses, and added 18 PD angles using the 20 PD doses.

Rationale for Change

There was an inconsistency between the angles listed in the surgical dose tables and the prism increments that the IXT1 Procedures Manual specifies should be used for measuring ocular

alignment. Prisms in 2 PD increments should be used for angles between 10 and 20 PD, therefore an angle between 15-20 PD could be measured as 16 PD or 18 PD, but not as 15 PD.

Protocol Change #5

Current Protocol
Control of exodeviation is measured at enrollment only.

Proposed Change
Control of exodeviation would be measured at masked exams as well as at enrollment (sections 1.3 and 4.5).

Rationale for Change
Although control of exodeviation will not be included in the definition of the primary outcome of surgical failure, it is felt worthwhile to evaluate whether patients who received one type of surgical procedure might have better control if their exodeviation persists or recurs, particularly if the primary analysis does not find a difference in surgical failure rates between the two procedures.

Protocol Change #6

Current Protocol
Currently the protocol is inconsistent with regard to whether treatment with overminus refractive correction is allowed during postoperative follow up. The protocol on post-operative treatment (section 4.1) indicates that any non-surgical treatment of any overcorrection, undercorrection, or deviations associated with diplopia is at investigator discretion at any time during the study. However, the guidelines for refractive correction during follow-up (section 5.3.2) indicate that deliberate overminus using refractive correction with more than 0.50 D of overminus will not be allowed.

Proposed Change
The prohibition of deliberate overminus with more than 0.50 D of overminus will be removed from the refractive correction guidelines during follow up (section 5.3.2), although it will be retained in the refractive correction guidelines for enrollment.

Rationale for Change
This change resolves a protocol inconsistency.

Protocol Change #7

Current Protocol
Mandatory treatment with prism is currently required for patients with a constant esotropia of *greater than* 6 PD at distance and near at 8 weeks, however the level of constant esotropia at distance and near which constitutes surgical failure at 6 months or later is *at least* 6 PD.

Proposed Change
Require mandatory treatment with prism at 8 weeks for patients with a constant esotropia of *at least* 6 PD at distance and near (sections 1.4, 4.1, and 4.4.1).

Rationale for Change

Although these concepts are different—i.e. what level of constant esotropia should receive mandatory prism treatment for patient safety, and what level is appropriate for determining surgical failure—it was felt it would be less confusing and easier for investigators to remember if the cutoffs used were identical.

Protocol Change #8

Current Protocol

The current protocol does not specify whether patients wearing prism and/or overminus should have clinical assessments performed with prism and/or overminus, or without.

Proposed Change

Clarified refractive correction to be used for testing during follow-up (section 4.3, 4.4, 4.5). Ocular alignment testing (and control assessments at masked exams) should be performed in current correction *without* any prism or deliberate overminus that has been prescribed. Stereoacuity testing and visual acuity testing should be performed in current correction *with* any prism or deliberate overminus that has been prescribed.

Rationale for Change

For ocular alignment, it was felt that the patient's true deviation should be assessed and that this would best be achieved by taking measurements in current correction but without prism and without overminus

For stereoacuity and visual acuity testing, it was felt that we should measure the patient's best stereoacuity and visual acuity, which for patients prescribed prism and/or deliberate overminus would likely be achieved with current correction including prism and/or deliberate overminus.

Protocol Change #9

Current Protocol

Protocol change #8 specifies that during follow up, stereoacuity testing should be performed with any prism or deliberate overminus that has been prescribed.

Proposed Change

At the 3-year visit, patients who are currently prescribed prism and/or deliberate overminus will have Preschool Randot Stereoacuity at near repeated *without* wearing prism or overminus (sections 4.5.3 and 6.3.1). This additional Preschool Randot retest without prism and without overminus should occur after all initial stereoacuity testing has been completed (ie. after the Titmus Fly at near) and before the control of exodeviation assessment. This testing without prism and overminus is for an exploratory analysis and is not considered in the determining whether the patient meets surgical failure criteria.

Rationale:

Although patients wearing prism will have stereoacuity measured with prism, is of interest to know whether a patient classified as a success would still be classified as a success if the patient had been measured without prism. Because 'success' only applies to the 3-year visit (whereas failure can be called at any visit from 6 months onward), we propose to measure stereoacuity

both with prism and without prism at the 3-year visit only. The with-prism measurement will count toward the primary outcome, and the without-prism measurement will be used in an exploratory analysis which would avoid calling a patient a success at 3-years on the basis of a better stereo that is enhanced by prism. The same logic should apply to patients wearing deliberate overminus—ie. stereoacuity should be measured with the overminus throughout the study but that it should be repeated without the overminus at the 3-year exam with this latter test used in the exploratory analysis.

This amendment also provides for the following minor protocol clarifications:

- Clarified guidelines for prescribing the spherical component of refractive correction (sections 2.2.1 and 5.3.2)
- Specified test distances for stereoacuity testing and for ocular alignment testing (sections 2.5, 4.3, 4.4, 4.5).
- Clarified refractive error eligibility criteria that treatment with prism or overminus lenses must be discontinued at least one week prior to enrollment (section 2.2.1).
- Clarified eligibility criteria that visual acuity in the worse eye must be '0.3 logMAR or better,' to eliminate confusion about whether 'at least 0.3 logMAR' meant at least 0.3 logMAR numerically (meaning worse acuity) or qualitatively (meaning better acuity) (sections 1.4 and 2.2.1).
- Clarified that hangback, hemi-hangback, and adjustable techniques will not be allowed for this protocol, however, the surgeon may make epi-scleral tickbites at the intended insertion site and then bring the sutures forward to take a standard scleral bite at the original insertion site (section 3.3).

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TABLE OF CONTENTS

CHAPTER 1: BACKGROUND AND SUMMARY

This study is being conducted by the Pediatric Eye Disease Investigator Group (PEDIG) and funded through a cooperative agreement from the National Eye Institute. It is one of a series of randomized trials and observational studies underway or planned that address management of intermittent exotropia.

1.1 Background

Intermittent exotropia (IXT) is the most common form of childhood onset exotropia with an incidence of 32.1 per 100,000 in children under 19 years of age.[2] Intermittent exotropia is characterized by an exotropia that is not constant and is mainly present when viewing at distance, but may also be present at near. Normal binocular single vision (BSV) is typically present at near when the exotropia is controlled, with evidence of normal (occasionally sub-normal) stereoacuity. Although the natural history of the condition is largely unknown, many children with IXT are treated using either surgical or non-surgical interventions. The rationale for intervention in childhood IXT is that extended periods of misalignment may lead to entrenched suppression, resulting in loss of BSV. Intervention may also aim to address the social effects caused by the appearance of misaligned eyes. Many children treated for IXT are currently treated surgically.[3-5]

There is poor agreement as to which type of surgery is most effective for the correction of IXT and the debate has long been related to differentiation between IXT sub-types. Based on distance-near angle disparity, IXT sub-types are classified as: 1) basic (similar magnitude of misalignment at distance and near); 2) true divergence excess (larger at distance); 3) pseudo divergence excess (initially larger at distance, but near angle increases following occlusion or with addition of plus lenses at near); 4) convergence insufficiency (larger at near). Basic and pseudo divergence excess appear to be the most common of the sub-types,[6] and are also the types for which there is most disagreement regarding the optimum surgical approach. The two most common procedures are bilateral lateral rectus recession (BLRrec) and unilateral lateral rectus recession combined with a medial rectus resection in the same eye (R&R). Traditionally, BLRrec has been advocated where there is a larger distance angle, and R&R where there is a similar angle at distance and near.[7,8] A survey of American strabismus surgeons published in 1990[9] found that the majority performed BLRrec for both basic and divergence excess types. Similarly, we found by polling our investigator group that the majority still perform a BLRrec for basic type IXT. Nevertheless, controversy still exists as to which of these surgical approaches is superior.[10] Advocates of the BLRrec procedure tend to hold that surgery should be based purely on the distance angle of deviation.[5,11] Proponents of R&R surgery suggest resection of the medial rectus best addresses the exodeviation at near.[7,12]

The proposed advantage of the R&R procedure is that resecting the medial rectus, with a possible longer term initial overcorrection, is necessary for a stable and superior long-term outcome. Nevertheless, those who favor the BLRrec procedure suggest that the more profound and prolonged initial overcorrection occurring with R&R is not only unnecessary, but may in fact be harmful. A persistent overcorrection may be associated with the development of diplopia, amblyopia, and loss of stereoacuity. On the other hand, critics of the BLRrec procedure suggest that long-term recurrence rates are higher. Poor motor outcomes are likely to require reoperation and therefore the long-term success rates of these surgeries have public health importance in terms of cost to society.

Evaluating initial and long-term surgical outcomes in the proposed RCT will answer questions regarding the failure rates of these surgeries and also provide needed data on the potential harm of each procedure.

Only one prospective randomized clinical trial addresses success rates of BLRrec versus R&R for IXT.[12] After between 12-15 months of follow up, 82% of 17 patients undergoing an R&R had a satisfactory outcome compared to 52% of 19 patients undergoing a BLRrec. Nevertheless, there are some important limitations of this previous study. The sample size was very small. The study population was a sub-group of patients with basic type IXT, excluding patients with basic IXT whose angle of deviation increased at far distance or following occlusion, thus limiting the generalizability of the results. In addition, outcomes were assessed unmasked, potentially biasing the results. One observational study[13] of 103 patients (90% of whom had basic type IXT) found 1-year success rates of 56% for BLRrec and 60% for R&R. A retrospective study[14] of 115 patients with basic type IXT reported success rates of 69% for BLRrec and 77% for R&R after an average of 15 months of follow up. Other studies comparing surgery types are limited not only by retrospective study design but also by inclusion of other types of exotropia, making it difficult to interpret results. In addition, many different criteria for success are used, precluding meaningful comparison of success rates between studies. This lack of evidence makes it very difficult to counsel parents of children with IXT regarding the likely success and complication rate of either procedure, limiting our ability to make informed management decisions. Establishing the respective failure rates through the proposed study will allow physicians to offer patients the type of surgery with the highest chance of long-term success, minimizing suboptimal results and repeat surgeries.

The present study is being conducted to compare the effectiveness of BLRrec with R&R for the surgical treatment of basic type and pseudo divergence excess type IXT.

1.2 Study Objective

To evaluate the effectiveness of bilateral lateral rectus muscle recession versus unilateral lateral rectus recession with medial rectus resection procedures for the treatment of basic type and pseudo divergence excess type intermittent exotropia

1.3 Synopsis of Study Design

Major Eligibility Criteria *(see sections 2.2 and 2.3 for a complete listing and definition of type of IXT)*

- Age 3 to < 11 years
- Intermittent exotropia (manifest deviation) meeting all of the following:
    - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
    - Exodeviation at least 10 PD at distance AND near by prism and alternate cover test (PACT)
    - Exodeviation at least 15 PD at distance OR near by PACT
    - Largest exodeviation at either distance, near, or remote distance between 15 and 50 PD (inclusive)
    - Basic type or pseudo divergence excess type (as defined in *section 2.3*)
- Stereoacuity of 400 arcsec or better at near by Preschool Randot stereotest (better of 2 measures)

- Visual acuity in the worse eye 0.3 logMAR or better (20/40 on ATS HOTV or 70 letters on E-ETDRS)
- No interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS testing)
- No hyperopia greater than +3.50 D spherical equivalent in either eye
- Absence of high AC/A ratio (exclude > 6:1)
- No previous intraocular surgery, strabismus surgery, or botulinum toxin treatment
- Investigator planning to perform surgery for correction of IXT

Sample Size

189 patients with basic type IXT with largest exodeviation between 15 and 40 PD by PACT at remote distance, distance, or near, and 189 patients with pseudo divergence excess type IXT with largest exodeviation between 15 and 40 PD by PACT at remote distance, distance, or near (total of 378 patients). Additional patients with exotropia > 40 PD to 50 PD will be enrolled during recruitment of the above sample size.

Treatment

Randomization (1:1) to surgical correction of IXT with a bilateral lateral rectus recession (BLRrec) or a unilateral lateral rectus recession with medial rectus resection (R&R)

Visit Schedule

- Enrollment
- Randomization (the day of surgery or the working day before surgery)
- Surgery
- 1 week ± 3 days from surgery
- 8 weeks ± 2 weeks from surgery
- 6 months ± 1 month from randomization (masked)
- 12 months ± 2 months from randomization (masked)
- 18 months ± 2 months from randomization (masked)
- 24 months ± 2 months from randomization (masked)
- 30 months ± 2 months from randomization (masked)
- 3-Year Primary Outcome Exam: 3 years ± 2 months from randomization (masked)

Ocular alignment and visual acuity will be tested at each visit. Control of the exodeviation will be assessed at enrollment and at all masked exams. Stereoacuity will be tested at all visits except the 1-week visit. Health-related quality of life will be assessed at baseline, at 6 months, and at 3 years after randomization.

Primary Analysis

As defined in the analysis plan, the primary analysis will consist of a treatment group comparison of the proportion of patients who meet criteria for failure at the 3-year outcome exam (*section 4.5.1*) among patients with largest baseline preoperative exodeviation between 15 and 40 PD by PACT at remote distance, distance, or near.

Separate analyses will be conducted within groups defined by IXT type:

- Basic type IXT
- Pseudo divergence excess type IXT

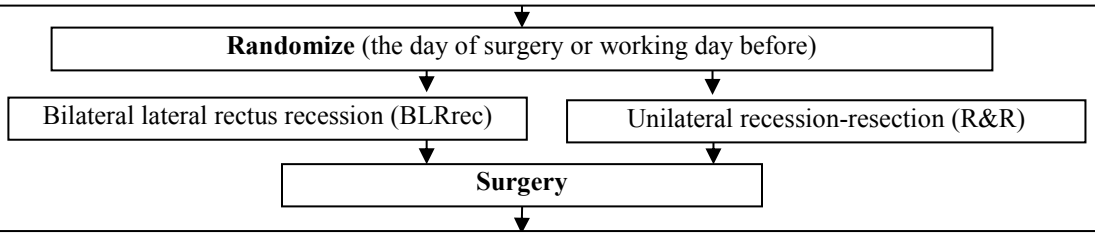
1.4 Study Flow Chart

Major Eligibility Criteria

- Age 3 to < 11years
- Intermittent exotropia (manifest deviation) meeting all of the following:
  - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
  - Exodeviation at least 10 PD at distance AND near by PACT
  - Exodeviation at least 15 PD at distance OR near by PACT
  - Largest exodeviation at either distance, near, OR remote distance between 15 and 50 PD (inclusive) by PACT
  - Basic type or pseudo divergence excess type (as defined in *section 2.3*)
- Stereoacuity of 400 arcsec or better at near by Preschool Randot Stereotest
- Visual acuity in the worse eye 0.3 l **NO** or better (20/40 by ATS HOTV for patients < 7 years or 70 letters on E-ETDRS for patients ≥ 7 years old)
- No interocular difference of visual acuity more than 0.2 logMAR (2 lines by ATS HOTV for patients < 7 years old or 10 letters by E-ETDRS for patients >=7 years old)
- No hyperopia greater than +3.50 D spherical equivalent in either eye
- Wearing appropriate spectacles or contact lenses for at least one week if refractive error meets refractive correction criteria
- Absence of high AC/A ratio (exclude >6:1)
- No previous strabismus surgery or botulinum toxin treatment
- No previous intraocular eye surgery or refractive surgery
- No ocular disorders which would reduce visual acuity (other than refractive error)
- No coexisting vertical deviation, oblique muscle dysfunction, and A or V pattern, if condition warrants vertical transposition of horizontal rectus muscles, oblique surgery, or vertical rectus muscle surgery
- No limitation of ocular rotations due to restrictive or paretic strabismus
- No significant neurological impairment such as cerebral palsy
- Investigator wishes to perform surgery for correction of IXT

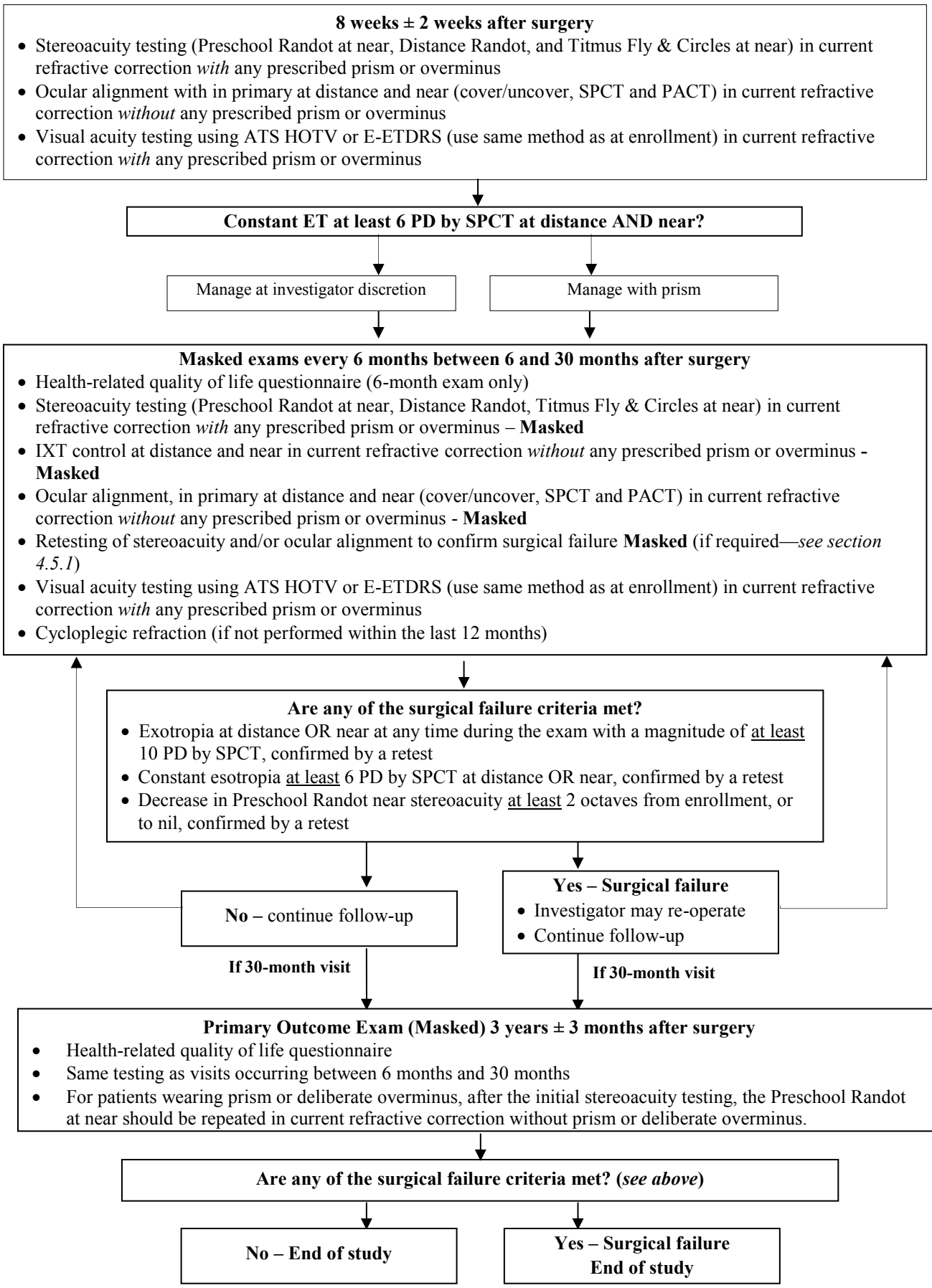
Enrollment Testing Procedures

- Health-related quality of life questionnaire
- Stereoacuity testing with current correction
  - Preschool Randot at near - if stereoacuity is worse than 40 arcsec, retest and use better of 2 measurements for eligibility
  - Distance Randot
  - Titmus Fly/Circles at near
- IXT control at distance and near
- Ocular alignment with current correction tested using cover/uncover, SPCT, and PACT, at distance, remote distance (PACT only), and near
- Visual acuity with current correction and using ATS HOTV (patients < 7 years old) or E-ETDRS (patients ≥ 7 years old)
- Ocular exam (if not done in last 6 months)
- Cycloplegic refraction (if not done in last 6 months)



1 week ± 3 days after surgery

- Ocular alignment in primary at distance and near (cover/uncover, SPCT and PACT) in current refractive correction *without* any prescribed prism or overminus
- Visual acuity testing using ATS HOTV or E-ETDRS (use same method as at enrollment) in current refractive correction *with* any prescribed prism or overminus


8 weeks ± 2 weeks after surgery
• Stereoacuity testing (Preschool Randot at near, Distance Randot, and Titmus Fly & Circles at near) in current refractive correction *with* any prescribed prism or overminus
• Ocular alignment with in primary at distance and near (cover/uncover, SPCT and PACT) in current refractive correction *without* any prescribed prism or overminus
• Visual acuity testing using ATS HOTV or E-ETDRS (use same method as at enrollment) in current refractive correction *with* any prescribed prism or overminus
Constant ET at least 6 PD by SPCT at distance AND near?
Manage at investigator discretion
Manage with prism
Masked exams every 6 months between 6 and 30 months after surgery
• Health-related quality of life questionnaire (6-month exam only)
• Stereoacuity testing (Preschool Randot at near, Distance Randot, Titmus Fly & Circles at near) in current refractive correction *with* any prescribed prism or overminus – **Masked**
• IXT control at distance and near in current refractive correction *without* any prescribed prism or overminus - **Masked**
• Ocular alignment, in primary at distance and near (cover/uncover, SPCT and PACT) in current refractive correction *without* any prescribed prism or overminus - **Masked**
• Retesting of stereoacuity and/or ocular alignment to confirm surgical failure **Masked** (if required—*see section 4.5.1*)
• Visual acuity testing using ATS HOTV or E-ETDRS (use same method as at enrollment) in current refractive correction *with* any prescribed prism or overminus
• Cycloplegic refraction (if not performed within the last 12 months)
Are any of the surgical failure criteria met?
• Exotropia at distance OR near at any time during the exam with a magnitude of at least 10 PD by SPCT, confirmed by a retest
• Constant esotropia at least 6 PD by SPCT at distance OR near, confirmed by a retest
• Decrease in Preschool Randot near stereoacuity at least 2 octaves from enrollment, or to nil, confirmed by a retest
No – continue follow-up
Yes – Surgical failure
• Investigator may re-operate
• Continue follow-up
If 30-month visit
If 30-month visit
Primary Outcome Exam (Masked) 3 years ± 3 months after surgery
• Health-related quality of life questionnaire
• Same testing as visits occurring between 6 months and 30 months
• For patients wearing prism or deliberate overminus, after the initial stereoacuity testing, the Preschool Randot at near should be repeated in current refractive correction without prism or deliberate overminus.
Are any of the surgical failure criteria met? (*see above*)
No – End of study
Yes – Surgical failure
End of study

CHAPTER 2: ENROLLMENT AND RANDOMIZATION

2.1 Eligibility Assessment and Informed Consent

A minimum of 378 subjects (189 with basic type IXT and 189 with pseudo divergence excess type IXT) are expected to be enrolled for the primary cohort (*section 6.1*), with a goal to enroll an appropriate representation of minorities. An additional 76 patients are expected to be enrolled for the secondary cohort (*section 6.3*) during recruitment for the primary cohort. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 474.

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

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

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

1. Age 3 to < 11 years
2. Intermittent exotropia (manifest deviation) meeting all of the following:
    - Intermittent exotropia at distance OR constant exotropia at distance and either intermittent exotropia or exophoria at near
    - Exodeviation at least 10 PD at distance AND near by PACT
    - Exodeviation at least 15 PD at distance OR near by PACT
    - Largest exodeviation at distance, near OR remote distance between 15 and 50 PD (inclusive) by PACT
    - Basic type or pseudo divergence excess type (as defined in *section 2.3*)
3. Stereoacuity of 400 arcsec or better at near by Preschool Randot stereotest (better of 2 measures if initial test shows worse than 40 arcsec)
4. Visual acuity in the worse eye 0.3 logMAR or better (20/40 by ATS HOTV for patients < 7 years old or 70 letters E-ETDRS testing for patients ≥ 7 years old)
5. No hyperopia greater than +3.50 D spherical equivalent in either eye
6. Patients must be wearing spectacles or contact lenses for at least one week if refractive error (based on cycloplegic refraction performed within 6 months prior to enrollment) meets any of the following:
    - Myopia > -0.50 D spherical equivalent in either eye
    - Anisometropia > 1.00 D spherical equivalent
    - Astigmatism > 2.00 D in either eye if ≤ 5 years old and > 1.50 D if > 5 years old

    Refractive correction for patients meeting the above refractive error criteria must meet the following guidelines:
    - Anisometropia spherical equivalent must be within 0.25 D of full correction.

- Astigmatism cylinder must be within 0.25 D of full correction and axis must be within 5 degrees of full correction.
- For hyperopia, the spherical component can be reduced at investigator discretion provided the reduction is symmetrical. Prescribing any refractive correction to yield lenses that are more myopic than -0.50 D spherical equivalent (SE) is considered deliberate overminus and is not allowed *at enrollment*. However, prescribing no correction or prescribing less than the full cycloplegic hyperopic correction (i.e., prescribing reduced plus) is not considered the same as overminusing for this protocol and is allowed because most patients without intermittent exotropia and hyperopic SE refractions in this range would not typically be prescribed a refractive correction.
- For myopia, the intent is to fully correct, but the spherical component can be undercorrected by 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 *at enrollment.*

Patients who have undergone treatment with prism or deliberate overminus refractive correction (as defined above) must have discontinued prism and/or any deliberate overminus for at least one week prior to enrollment.

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

7. No atropine use within the last week
8. Gestational age > 34 weeks
9. Birth weight > 1500 grams
10. Investigator plans to perform surgery, is willing to perform either surgical procedure, and is not planning to use adjustable sutures.
11. Parent understands protocol, has agreed to surgery, and is willing to accept randomization to one-eye surgery or two-eye surgery
12. Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff
13. Relocation outside of area of an active PEDIG site within next 3 years is not anticipated

2.2.2 Exclusion Criteria

1. Coexisting vertical deviation, oblique muscle dysfunction, DVD, or A or V pattern, any of which the investigator plans to address with vertical transposition of horizontal rectus muscles, oblique surgery, or vertical rectus muscle surgery, i.e., only small vertical deviations, oblique muscle dysfunction, DVD, and A or V patterns *not* requiring surgery are allowed
2. Limitation of ocular rotations due to restrictive or paretic strabismus
3. Craniofacial malformations affecting the orbits
4. Interocular visual acuity difference of more than 0.2 logMAR (2 lines on ATS HOTV for patients 3 to < 7 years old or 10 letters on E-ETDRS for patients ≥ 7 years old) and/or investigator plans to initiate amblyopia treatment at this time.

5. High AC/A ratio (exclude > 6:1 by gradient method)
6. Prior strabismus surgery or botulinum toxin injection
7. Ocular disorders that would reduce visual acuity (except refractive error)
8. Prior intraocular or refractive surgery
9. Significant neurological impairment such as cerebral palsy. Patients with mild speech and/or learning disabilities are eligible.
10. Investigator planning to change refractive correction at this time (if the patient is otherwise eligible, the investigator should consider prescribing refractive correction and bringing the patient back at a later time for enrollment).

2.3 Determination of IXT Type

IXT will be classified (*see classification below*) at enrollment prior to randomization as:

- Basic Type
- Pseudo Divergence Excess Type

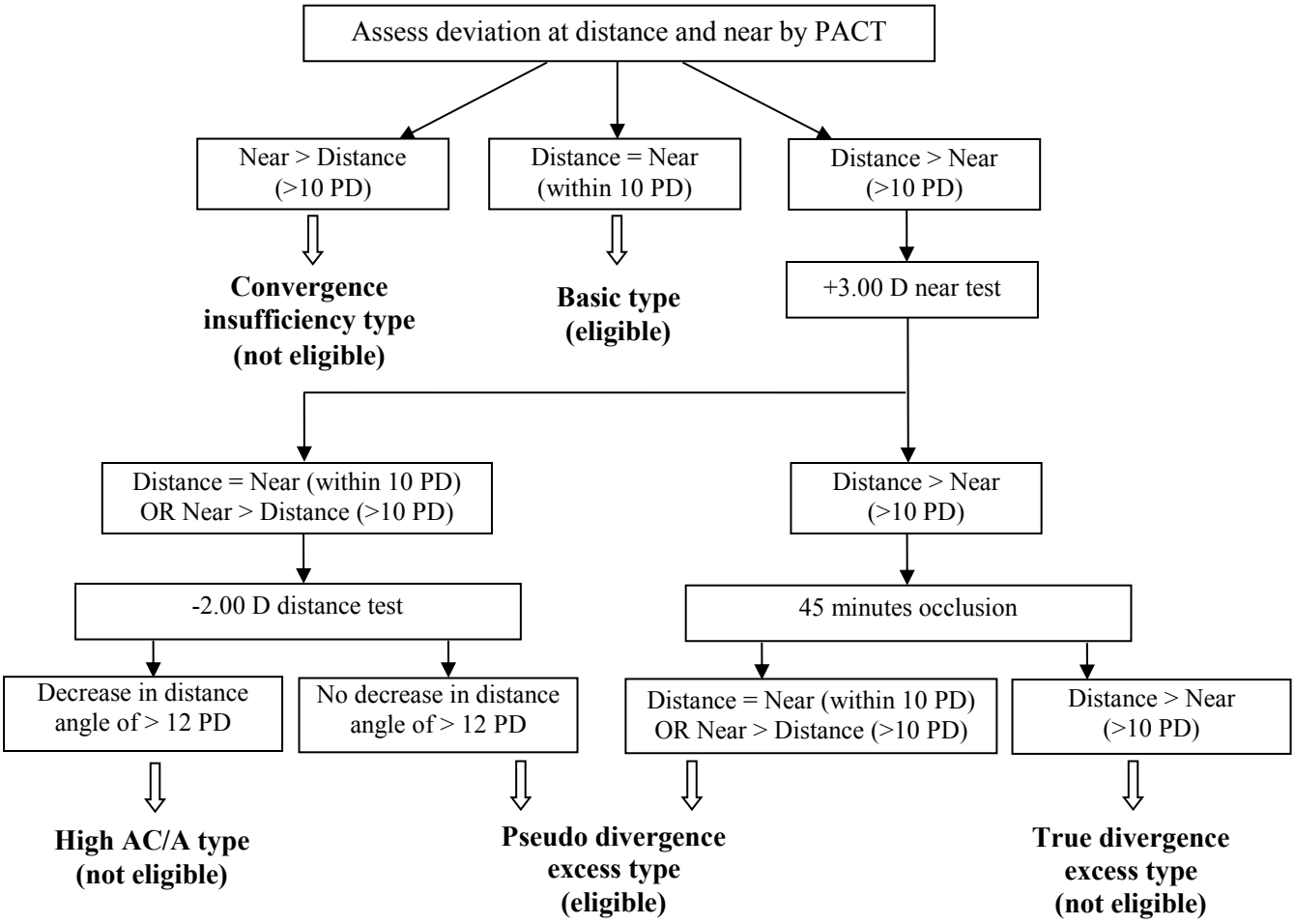
The following types of IXT are not eligible:

- True Divergence Excess Type
- Convergence Insufficiency Type
- High AC/A Type

Classification of IXT type will be done as follows (*also see flowchart on next page*):

Using the PACT at distance and near:

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



2.4 Historical Information

Historical information elicited will include the following: date of birth, gender, race, ethnicity, prior treatment, and spectacle correction. In addition, investigators will be asked to provide the reason(s) for performing surgery.

2.5 Examination Procedures at the Enrollment Visit

1. Health-Related Quality of Life Questionnaire: Health-related quality of life (HRQOL) will be assessed using the Intermittent Exotropia Questionnaire (IXTQ).[15] This questionnaire consists of 3 components:
    1. Child questionnaire (for children ages 5 years or older) – consists of 12 items which assess how the child feels about his/her eye condition.
        - The version for children aged 5 to < 8 years has a three-level response scale (not at all, sometimes, a lot) and is administered by clinical staff either verbally or using a matching card.
        - The version for children aged 8 years and older has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered. However, it may be administered verbally by clinical staff if the child cannot read the questionnaire by him- or herself.

- If possible, children should be positioned such that they are unable to view their parents during testing and parents should be advised not to influence their child's responses.
- Children 4 years and younger will not complete a child questionnaire.

2. Parent proxy questionnaire – consists of 12 items which assess how the parent feels the child's eye condition affects the child.
   - The questionnaire has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered.
3. Parental questionnaire – consists of 17 items which assess how the child's eye condition affects the parent.
   - The questionnaire has a five-level response scale (never, almost never, sometimes, often, almost always) and is self-administered.

2. Stereoacuity Testing: stereoacuity will be assessed in current refractive correction using the following:
   - Preschool Randot stereotest at near (performed at 40 cm): If stereoacuity is worse than 40 arcsec, it must be retested and the better of the 2 measurements will be used for eligibility.
   - Distance Randot stereotest (performed at 3 meters)
   - Titmus Fly & Circles stereotest at near (performed at 40 cm) (note: Animals are not tested)

   Stereoacuity should be tested before any other clinical testing. If stereoacuity is not tested first, the patient must take a 10 minute break following any dissociative testing (e.g., visual acuity or ocular alignment) prior to testing stereoacuity.
3. Control of exodeviation: Control of exodeviation will be measured in current refractive correction at distance and near using the Office Control Score.[16]
   - Distance (6 meters) - fixating on an accommodative target such as a video for younger children or reading optotype letters for older children
   - Near (1/3 meter – fixating on Lang-near viewing stick or similar accommodative target)

   The scale below applies to both distance and near.

   Intermittent Exotropia Control Scale[16]

   5 = Constant Exotropia
   4 = Exotropia > 50% of the 30-second period before dissociation
   3 = Exotropia < 50% of the 30-second period before dissociation
   2 = No exotropia unless dissociated, recovers in > 5 seconds
   1 = No exotropia unless dissociated, recovers in 1-5 seconds
   0 = No exotropia unless dissociated, recovers in < 1 second (phoria)

   - Levels 5 to 3 are assessed during a 30-second period of observation first at distance fixation and then assessed at near fixation for another 30-second period.
   - If no exotropia is observed during the 30-second period of observation, levels 2 to 0 are then graded as the worst of three rapidly successive trials:
     1. An occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to become re-established.
     2. The left eye is then occluded for a 10-second period and the time to re-establish fusion is similarly measured.

3. A third trial of 10-second occlusion is performed, covering the eye that required the longest time to re-fuse.

- The worse level of control observed following the three 10-second periods of occlusion should be recorded. If the patient has a micro-esotropia by SPCT but an exodeviation by PACT, the scale applies to the exodeviation.
- Testing of control must be performed by a pediatric ophthalmologist, pediatric optometrist, or a certified orthoptist.
- Testing must be done prior to dissociative testing or at least 10 minutes after such testing.

4. Ocular alignment testing:
   - Strabismic deviations will be assessed in current refractive correction (either spectacles, contact lenses, or a trial frame) by the cover/uncover test and then measured with the Simultaneous Prism and Cover Test (SPCT) (if tropia is of sufficient duration to measure) and Prism and Alternate Cover Test (PACT) in primary position at near (1/3 meter), distance (6 meters) and remote distance (at least 50 feet, e.g., out the window or down a long hallway) (PACT only) as outlined in the IXT Testing Procedures Manual.
   - The deviation will be recorded as constant if a manifest tropia is present 100% of the time during the examination, determined by at least 3 cover/uncover tests (one must be before any dissociation), or as intermittent if a manifest tropia is present (including after dissociation) but not 100% of the time during the entire exam. The magnitude of the deviation may change (vary) independently of the frequency of the deviation; frequency of tropia (constant vs. intermittent) is determined solely by whether the manifest tropia is present all or some of the time, including after dissociation. If a tropia is not observed at any time but a phoria is present, then the deviation will be recorded as not tropic (phoric only). If no deviation is present at any time, 'no deviation' will be recorded.
     - If the child appears to have a constant tropia but shows excellent stereoacuity that may be inconsistent with the diagnosis of constant tropia, the examiner should look over the child's polarized glasses to determine whether the child is indeed constantly tropic (by direct observation by cover/uncover test).
   - The deviating eye will be recorded as "right", "left", or "alternates."
   - Testing will be performed following control of exodeviation testing and prior to any cycloplegia.
   - Ocular motility will be assessed including: ductions, oblique muscle dysfunctions, dissociated vertical deviations, and nystagmus.
   - Ocular alignment testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
5. Visual Acuity Testing: Visual acuity testing will be done with current refractive correction without cycloplegia by a certified examiner with the Electronic Visual Acuity tester (EVA) using the ATS single surround HOTV protocol for patients < 7 years old and using the E-ETDRS for patients ≥ 7 years old. The protocol for conducting the visual acuity testing is described in the ATS Testing Procedures Manual. For each patient, the same visual acuity testing protocol used at enrollment will be used throughout the study.
6. Ocular Examination as per investigator's clinical routine (if not performed within 6 months)
7. Cycloplegic Refraction (if not performed within 6 months)
   - If refractive error as measured by cycloplegic refraction meets any of the following, then the patient must be wearing spectacles or contact lenses for at least a week:
     - Myopia > -0.50 D spherical equivalent in either eye

- Anisometropia > 1.00 D spherical equivalent
- Astigmatism > 2.00 D astigmatism in either eye if ≤ 5 years old and > 1.50 D if > 5 years old

2.6 Randomization

Randomization will be done on the day of surgery or the working day before surgery, to minimize potential treatment-group-related patient withdrawals between randomization and surgery.

Patients enrolled in the study will be randomized (1:1) to receive surgical correction of their IXT by one of the 2 following surgical procedures:

1. Bilateral lateral rectus recessions (BLRrec)
2. Unilateral lateral rectus recession with medial rectus resection (R&R) - a unilateral lateral rectus recession combined with a medial rectus resection in the same eye. Choice of eye at investigator discretion based on any interocular difference, position under anesthesia, fixation preference, or forced duction testing. Reason for choice of eye will be recorded.

The Jaeb Center will construct a separate Master Randomization List using a permuted block design stratified by site and cohort type (patients with basic type IXT with baseline angle size 15-40 PD, patients with pseudo divergence excess type IXT with baseline angle size 15-40 PD, all other patients) which will specify the order of treatment group assignments. A patient is officially enrolled when the website randomization process is completed.

Patients in whom the magnitude of the largest of the most recent distance, near, and remote distance angles has decreased to <15 PD or increased to >50 PD before surgery will be dropped from the study if they have not yet been randomized. If such patients have already been randomized, it is at investigator discretion whether to perform surgery and what type of surgical method to perform (i.e. BLRrec, R&R, or any other type of procedure).

Patients not randomized within 12 months of enrollment will be dropped from the study.

2.7 Repeat Enrollment Visit

If surgery is delayed for any reason to a date more than 60 days from the enrollment visit, the visit must be repeated. All examination procedures listed in *section 2.5* must be repeated at this visit. For surgeries occurring within 60 days of enrollment, the investigator has the option of repeating the alignment measurements prior to surgery—if repeated, the measurement used to determine surgical dose will be recorded on the Randomization Form.

CHAPTER 3: SURGICAL TREATMENT

3.1 Surgery Timing

Once randomized, the investigator is required to perform the assigned surgery type the same day or the next working day.

In the rare case that surgery is cancelled after randomization, surgery should be rescheduled within 60 days. For surgeries occurring within 60 days of enrollment, the investigator has the option of repeating the alignment measurements prior to surgery. If surgery is not performed within 60 days, the enrollment exam must be repeated (*section 2.7*).

If a patient has been randomized but the magnitude of the largest of the most recent distance, near, and remote distance angles has decreased to <15 PD or increased to >50 PD before surgery, it is at investigator discretion whether to perform surgery and what type of surgical method to perform (i.e., BLRrec, R&R, or any other type of procedure).

If a patient has been randomized, even if surgery is not performed, the patient will remain in the study and will complete all follow-up visits between 6 months and 3 years from randomization.

3.2 Surgical Treatment

Each patient is randomly assigned to one of the two surgical procedures.

1. Bilateral lateral rectus recessions (BLRrec)
2. Unilateral lateral rectus recession with medial rectus resection (R&R) – a unilateral lateral rectus recession combined with a medial rectus resection in the same eye. Choice of eye is at investigator discretion based on any interocular difference, position under anesthesia, fixation preference, or forced duction testing. Reason for choice of eye will be recorded.

3.3 Surgical Dose

The magnitude of deviation for which to perform surgery will be the largest preoperative deviation recorded at near, distance, or remote distance fixation by PACT. Data on this deviation will be entered on the Randomization Form. The recommended surgical doses are listed in Table 1 and Table 2, and will be generated as part of the randomization report. For recessions, the measurement of surgical dose should be made from the insertion of the muscle after muscle disinsertion. For resections, the measurement of surgical dose should be made from the insertion of the muscle prior to muscle disinsertion. Surgeons may adjust the surgical dose within 1.0 mm for each muscle at their discretion to account for individual patient variables, such as lateral incomitance and age.

Hangback, hemi-hangback, and adjustable techniques will not be allowed for this protocol, however, the surgeon may make epi-scleral tickbites at the intended insertion site and then bring the sutures forward to take a standard scleral bite at the original insertion site.

The target deviation, actual surgical dose, and any reasons for departure from the recommended dose tables will be recorded on the Surgery Form. Any complications during surgery will be recorded.

Table 1: Bilateral lateral rectus recession (BLRrec):

Angle of largest deviation	Amount to recess each LR
16 PD	4.0 mm
18 PD	5.0 mm
20 PD	5.0 mm
25 PD	6.0 mm
30 PD	7.0 mm
35 PD	7.5 mm
40 PD	8.0 mm
45 PD	8.5 mm
50 PD	9.0 mm

LR = lateral rectus

Table 2: Unilateral lateral rectus recession with medial rectus resection (R&R):

Angle of largest deviation	Amount to recess LR	Amount to resect MR
16 PD	4.0 mm	3.0 mm
18 PD	5.0 mm	4.0 mm
20 PD	5.0 mm	4.0 mm
25 PD	6.0 mm	5.0 mm
30 PD	7.0 mm	5.5 mm
35 PD	7.5 mm	6.0 mm
40 PD	8.0 mm	6.5 mm
45 PD	8.5 mm	6.5 mm
50 PD	9.0 mm	7.0 mm

LR = lateral rectus MR = medial rectus

CHAPTER 4: FOLLOW-UP

4.1 Treatment

Initial treatment consists of the randomly-assigned surgery as described in chapter 3.

Following the surgery, nonsurgical treatment of any overcorrection, undercorrection, or deviations associated with diplopia is at investigator discretion at any time during the study, with the following stipulation:

- If at the 8 week visit a constant esotropia at least 6 PD by SPCT at distance and near is present, the condition must be managed with prism (*section 4.4.1*).

Reoperation or treatment with botulinum toxin is not permitted during the first 6 months following surgery. After the 6-month exam, a patient may undergo reoperation or treatment with botulinum toxin only after criteria for surgical failure are met (*section 4.5.1*).

4.2 Follow-up Visit Schedule

Follow-up visits will be conducted at the following times:

- 1 week ± 3 days after surgery
- 8 weeks ± 2 weeks after surgery
- 6 months ± 1 month after randomization (masked)
- 12 months ± 2 months after randomization (masked)
- 18 months ± 2 months after randomization (masked)
- 24 months ± 2 months after randomization (masked)
- 30 months ± 2 months after randomization (masked)
- 3-Year Primary Outcome Exam: 3 years ± 2 months (masked)

4.3 1-Week Follow-up Exam

The 1-week follow-up exam will be 1 week ± 3 days following surgery.

At this visit, the following will occur:

- Ocular alignment in the primary position using cover/uncover, SPCT (if tropia is of sufficient duration to measure), and PACT, both at distance (6 meters) and near (1/3 meter) fixations (*section 2.5*)
    - Testing must be performed in current refractive correction.
        - If prism is currently prescribed, ocular alignment testing should be performed *without* prism.
        - If deliberate overminus is currently prescribed, ocular alignment testing should be performed in trial frames *without* the overminus component of the prescription but which correct the remaining refractive error to within study guidelines.
    - Testing must be performed without cycloplegia.
- Visual acuity by the same testing method used at enrollment
    - Testing must be performed in current refractive correction.
        - If prism is currently prescribed, visual acuity testing should be performed *with* prism.
        - If deliberate overminus is currently prescribed, visual acuity testing should be performed *with* the overminus correction.

- If visual acuity is found to be reduced by 0.2 logMAR or more (2 lines or 10 letters) from the previous visit and the patient is wearing a Fresnel prism, visual acuity should be retested in trial frames.
- Recording of any surgical or post-surgical complications.

4.4 8-Week Follow-up Exam

The 8-week follow-up exam will be 8 weeks ± 2 weeks following surgery. Prior to the patient's examination, spectacle correction will be verified using a lensometer. For patients wearing contact lenses, a dry over-refraction (i.e., non-cycloplegic retinoscopy) should be performed.

At this visit, the following procedures will occur in the specified order:

1. Stereoacuity - stereoacuity will be assessed using the following as in *section 2.5*:
   - Preschool Randot stereotest at near (performed at 40 cm)
   - Distance Randot stereotest (performed at 3 meters)
   - Titmus Fly & Circles stereotest at near (performed at 40 cm) (note: Animals are not tested)

   Testing must be performed in current refractive correction.
   - If prism is currently prescribed, stereoacuity testing should be performed *with* prism.
   - If deliberate overminus is currently prescribed, stereoacuity testing should be performed *with* the overminus correction.

   In the case of a protocol testing order violation, stereoacuity should be performed 10 minutes after any dissociation.
2. Ocular alignment in the primary position using cover/uncover, SPCT (if tropia is of sufficient duration to measure), and PACT, at both distance (6 meters) and near (1/3 meters) fixations (*section 2.5*).
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, ocular alignment testing should be performed *without* prism.
     - If deliberate overminus is currently prescribed, ocular alignment testing should be performed in trial frames *without* the overminus component of the prescription but which correct the remaining refractive error to within study guidelines.
   - Testing must be performed without cycloplegia.
3. Visual acuity by the same testing method used at enrollment
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, visual acuity testing should be performed *with* prism.
     - If deliberate overminus is currently prescribed, visual acuity testing should be performed *with* the overminus correction.
   - If visual acuity is found to be reduced by 0.2 logMAR or more (2 lines or 10 letters) from the previous visit, and the patient is wearing a Fresnel prism, visual acuity should be retested in trial frames.
   - If visual acuity is found to be reduced by 0.2 logMAR or more (2 lines or 10 letters) from the previous visit (after removal of Fresnel prism if applicable), a cycloplegic refraction must be performed and visual acuity retested in current refractive correction based on the cycloplegic refraction

Any additional post-surgical complications which have been recognized since the 1-week visit will be recorded.

4.4.1 Management of Esotropia and Diplopia at the 8-week Exam

At the 8-week exam:

- Constant esotropia at least 6 PD by SPCT at distance AND near must be managed with prism (either ground-in or Fresnel Press-On Optics; however, the study will only provide temporary press-on prisms). The amount of prism prescribed should be the minimum amount of prism needed to neutralize the angle. At each subsequent visit, an attempt should be made to reduce or discontinue prism. Despite initiation of treatment with prism, patients will not be considered a surgical failure at the 8-week exam.
    - Treatment of any esotropia greater than 6 PD that cannot be managed with prism should be discussed with the protocol chair. If a second surgical treatment is considered, this should be discussed with the protocol chair.
- Any other esotropia, exotropia, or diplopia can be managed with nonsurgical treatment at investigator's discretion *(section 4.1*).

4.5 Masked Exams at Six-month Intervals from Six Months to 3 Years

The six masked exams are timed every 6 months from randomization as follows:

- 6 months ± 1 month after randomization
- 12 months ± 2 months after randomization
- 18 months ± 2 months after randomization
- 24 months ± 2 months after randomization
- 30 months ± 2 months after randomization
- 3 years ± 2 months after randomization (primary outcome exam)

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

At these visits, the following testing procedures will occur in the specified order:

1. Health-related quality of life questionnaires (6-month and 3-year visits only)
2. Stereoacuity (masked) - stereoacuity will be assessed in current refractive correction, with prism if applicable, using the following as in *section 2.5 and 4.5.2*:
    - Preschool Randot stereotest at near (performed at 40 cm)
    - Distance Randot stereotest (performed at 3 meters)
    - Titmus Fly & Circles stereotest at near (performed at 40 cm) (note: Animals are not tested)

    Testing must be performed in current refractive correction.
    - If prism is currently prescribed, stereoacuity testing should be performed *with* prism.
    - If deliberate overminus is currently prescribed, stereoacuity testing should be performed *with* the overminus correction.

    In the case of a protocol testing order violation, stereoacuity should be performed 10 minutes after any dissociation.
3. Control of exodeviation: Control of exodeviation will be measured at distance (6 meters) and near (1/3 meter) using the Office Control Score[16] as described in section 2.5.

- Testing must be performed in current refractive correction.
  - If prism is currently prescribed, testing should be performed *without* prism.
  - If deliberate overminus is currently prescribed, testing should be performed in trial frames *without* the overminus component of the prescription but which correct the remaining refractive error to within study guidelines.

4. Ocular alignment (masked) in the primary position using cover/uncover, SPCT (if tropia is of sufficient duration to measure), and PACT, at both distance (6 meters) and near (1/3 meter) fixations (*sections 2.5 and 4.5.2*).
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, ocular alignment testing should be performed *without* prism.
     - If deliberate overminus is currently prescribed, ocular alignment testing should be performed in trial frames *without* the overminus component of the prescription but which correct the remaining refractive error to within study guidelines.
   - Testing must be performed without cycloplegia.
5. Retesting of stereoacuity and/or ocular alignment to confirm surgical failure (masked) (if required)
   - If any of the surgical failure criteria appear to be met (*section 4.5.1*) based on initial testing, the criterion met will be retested by a masked examiner (*section 4.5.2)*.
   - All retesting should be performed at least 10 minutes after the initial ocular alignment testing.
6. Visual acuity in current refractive correction (without prism if worn) by the same testing method used at enrollment
   - Testing must be performed in current refractive correction.
     - If prism is currently prescribed, visual acuity testing should be performed *with* prism.
     - If deliberate overminus is currently prescribed, visual acuity testing should be performed *with* the overminus correction.
   - If visual acuity is found to be reduced by 0.2 logMAR from the previous visit and the patient is wearing a Fresnel prism, visual acuity should be retested in trial frames.
   - If visual acuity is found to be reduced by 0.2 logMAR or more (2 lines or 10 letters) from the previous visit (after removal of Fresnel prism if applicable), a cycloplegic refraction must be performed and visual acuity retested in current refractive correction based on the cycloplegic refraction.
7. Cycloplegic refraction if not performed within the last 12 months
   - Management of refractive error is subject to the guidelines in *section 5.3*.

In addition, the following will be recorded:

- Any nonsurgical treatment of exotropia, esotropia or symptomatic diplopia (e.g., prism)
- Any treatment of amblyopia [interocular visual acuity difference of more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS) and worse eye acuity of worse than 0.3 logMAR (20/40 on ATS HOTV or 70 letters on E-ETDRS]
- Any change in refractive correction

Treatment can be prescribed as follows:

- Nonsurgical treatment of any overcorrection, undercorrection, or deviations associated with diplopia is at investigator discretion.
- If any of the surgical failure criteria are met (*section 4.5.1*), the investigator may elect to reoperate (*section 4.7*). If none of the surgical failure criteria are met, the investigator should not reoperate.

All patients should continue in follow up through 3-years, regardless of whether they undergo reoperation.

4.5.1 Surgical Failure Criteria

Patients will be considered a surgical failure if at any visit occurring 6 months or later any of the following failure criteria are present by masked examiner testing (section 4.5.2)*:

1. Exotropia at distance OR near at any time during the exam (i.e., can be constant or intermittent; determined by a cover/uncover test) with a magnitude of at least 10 PD by SPCT, confirmed by a retest
2. Constant esotropia at distance OR near (determined by at least 3 cover/uncover tests—one must be before any dissociation) with a magnitude of at least 6 PD by SPCT, confirmed by a retest
3. Decrease in Preschool Randot near stereoacuity at least 2 octaves (at least 0.6 log arcsec) (*see Table 3*) from the enrollment measurement, or to nil, confirmed by a retest

Table 3: Preschool Randot Stereotest

Baseline Stereoacuity, in arcsec	Level needed at follow up visit to meet surgical failure criteria, in arcsec
40”	200” or worse
60”	400” or worse
100”	400” or worse
200”	800” or worse
400”	Nil

*Note that both the initial testing and the retest must be performed by a masked examiner (*section 4.5.2*). If a patient appears to have met one or more of the above surgical failure criteria but the retest(s) do not confirm that at least one criterion is met, the patient is not considered to be a surgical failure.

Patients will also be considered a surgical failure if they undergo a second surgery or treatment with botulinum toxin at any time during the study.

All patients will continue to return for all protocol-specified follow-up exams regardless of whether surgical failure criteria are met.

4.5.2 Masked Examiner Testing

Stereoacuity and ocular alignment testing at the visit must be performed by a masked examiner.

If retesting is needed, retesting should be performed at least 10 minutes after the initial ocular alignment testing.

- First, if the surgical failure criterion related to a drop in Preschool Randot stereoacuity at near appears to be met (*section 4.5.1*); the masked examiner will retest Preschool Randot stereoacuity at near.
- Second, if either of the surgical failure criteria related to presence of a tropia appear to be met (*section 4.5.1*), the masked examiner will retest cover/uncover testing and SPCT at distance and near (if tropia is of sufficient duration to measure).

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

4.5.3 Patients Wearing Prism and/or Deliberate Overminus at 3-Years

In addition to the assessments listed in section 4.5, *at the 3-year masked exam only*, patients who are currently prescribed prism and/or deliberate overminus will have Preschool Randot Stereoacuity at near repeated in current refractive correction but *without* prism or overminus. This additional Preschool Randot retest without prism and without overminus should occur after all initial stereoacuity testing has been completed (ie. after the Titmus Fly at near) and before the control of exodeviation assessment. This testing without prism and overminus is for an exploratory analysis only (section 6.3.1) and is not considered in determining whether the patient meets surgical failure criteria for the primary analysis.

4.6 Additional Visits

Investigators may schedule additional visits at their own discretion. If the investigator feels the patient has met surgical failure criteria, then he/she must arrange a masked examiner testing (*section 4.5.2*) to confirm surgical failure criteria before performing additional surgery. If the masked exam does not confirm that the surgical failure criteria have been met, additional surgery should not be performed.

The patient will continue to follow the regular follow-up exam schedule following this additional visit.

4.7 Re-operation

Re-operations of IXT and treatment with botulinum toxin for IXT are allowed during the study after completion of the first 6-month follow-up exam, if the patient meets the surgical failure criteria at any follow-up exam 6 months or later (*see section 4.5.1*). The exception is patients with non-manageable esotropia following the 8-week exam who may require a second surgery before the 6-month exam. Any reoperation or botulinum toxin treatment prior to the 6-month exam must be discussed with the protocol chair. All patients undergoing either surgery a second time or treatment with botulinum toxin will be considered a surgical failure for the primary analysis. The reason for the re-operation or botulinum toxin treatment must be recorded and the patient will continue to return for all protocol-specified follow-up exams.

4.8 Treatment of Amblyopia

Treatment of amblyopia is allowed at investigator discretion at any time during follow up if a patient has an interocular difference of visual acuity more than 0.2 logMAR (2 lines on ATS HOTV or 10 letters on E-ETDRS) with a worse eye visual acuity of worse than 0.3 logMAR (20/40 on HOTV or 70 letters on E-ETDRS). The method of treatment is at investigator

discretion but cannot include atropine or overplus spectacle lenses. Any amblyopia treatment will be recorded.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

5.1 Contacts by the Jaeb Center for Health Research

The Jaeb Center will maintain direct contact with the parents of each patient at least 2 times per year. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the patient and/or family and to help coordinate scheduling of the outcome examinations. Additional contacts will be made if necessary for the scheduling of follow-up visits.

5.2 Patient Withdrawals

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

5.3 Management of Refractive Error

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

For patients whose refractive error meets criteria for requiring a refractive correction (*section 5.3.1*), the correction prescribed should meet the refractive correction guidelines (*section 5.3.2)*.

For patients whose refractive error does not meet the criteria for a required correction (*section 5.3.1*), it is at investigator discretion whether to prescribe correction; however, if refractive correction is prescribed, it should meet the refractive correction guidelines (*section 5.3.2)*.

5.3.1 Refractive Error Requiring Correction

The following are the criteria for requiring refractive error correction:

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

5.3.2 Refractive Correction Guidelines

The following are the guidelines for refractive correction which apply to patients meeting criteria for requiring refractive error correction *(section 5.3.1)* and to any other patient wearing refractive correction.

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

- The spherical component can be reduced by investigator discretion provided the reduction is symmetrical and results in residual (i.e., uncorrected) spherical equivalent refractive error that does not exceed +3.50D hyperopia or -0.50 D myopia.

The study will not pay for spectacles required at enrollment, but will pay for lens changes and/or new spectacles which are needed during follow up to keep the correction within the study guidelines *(section 5.3)*. All other new spectacles and/or lens changes will not be paid for by the study, as they are part of normal care. The study will not pay for contact lenses.

5.4 Risks

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

5.4.1 Risks of Examination Procedures

The procedures in this study are part of routine eye care practice in the United States and as part of this study they pose no additional known risks.

5.4.2 Risks of Surgery

All surgical procedures are standard care. The risks of surgery in this study are no different than surgery performed outside of the study.

There is a very rare risk of death (less than 1 in 100,000), there is a very rare risk of loss of vision, and there is a risk of overcorrection or undercorrection which could require subsequent surgeries.

5.4.3 Risk Assessment

It is the investigators' opinion that the protocol's level of risk falls under DHHS 46.404 which is research not involving greater than minimal risk.

5.5 Reporting of Adverse Events

Each site is responsible for informing its IRB of serious treatment-related adverse events and for abiding by any other reporting requirements specific to his or her IRB. Data on the complications of the study treatments will be tabulated regularly by the Coordinating Center for review by the Steering Committee. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

5.6 Discontinuation of Study

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

5.7 Travel Reimbursement

The parent/guardian of each patient will be compensated $30 per visit for completion of each protocol-specified follow-up visit, for a maximum of $240. If there are extenuating circumstances, and the patient is unable to complete study visits without additional funds due to travel costs, additional funds may be provided.

5.8 Study Costs

The subject or his/her insurance will be responsible for the costs that are considered standard care. This includes the initial examination, all follow up visits, all surgical procedures, and all costs involved in managing surgical complications.

The study will not pay for spectacles required at enrollment, but will pay for lens changes and/or new spectacles which are needed during follow up to keep the correction within the study guidelines *(section 5.3)*. All other new spectacles and/or lens changes will not be paid for by the study, as they are part of normal care. The study will not pay for contact lenses.

The study will provide temporary press-on prisms and spectacles to mount the prism (if needed and the patient isn't wearing glasses).

CHAPTER 6: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

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

6.1 Primary Data Analysis

The primary analysis cohort consists of patients whose largest exodeviation by PACT at distance, near, or remote distance at the enrollment exam is between 15 and 40 PD inclusive.

The primary analysis will be a treatment group comparison of the proportion of patients with surgical failure by 3 years (*section 6.1.1.)*.The primary analysis is stratified by IXT type (basic type and pseudo divergence excess type).

The cumulative proportion of patients meeting criteria for failure by 3 years will be obtained using the Kaplan-Meier method and compared between treatment groups using the Z test. This will allow patients who drop out prior to 3 years to contribute to the estimation of the proportion of surgical failure at 3 years. In this analysis, all patients who meet surgical failure criteria prior to 3 years will be counted as failures at the first visit at which surgical failure criteria are met. The primary analysis will follow the intent-to-treat principle.

6.1.1 Classification of Outcome

At the 3-year visit, each patient's condition will be classified as either surgical failure, success, or indeterminate as follows:

Failure = ANY of the following criteria are met at a visit 6 months or later:

1. Exotropia at distance OR near at any time during the exam (i.e., can be constant or intermittent; determined by a cover/uncover test) with a magnitude of <u>at least</u> 10 PD by SPCT, confirmed by a retest
2. Constant esotropia at distance OR near (determined by at least 3 cover/uncover tests—one must be before any dissociation) with a magnitude of <u>at least</u> 6 PD by SPCT, confirmed by a retest
3. Decrease in Preschool Randot near stereoacuity <u>at least</u> 2 octaves (<u>at least</u> 0.6 log arcsec) (*see Table 3*) from the enrollment measurement, or to nil, confirmed by a retest
4. Reoperation or treatment with botulinum toxin

Success = ALL of the following criteria are met at the 3-year visit:

1. Exodeviation less than 10 PD (tropia or phoria) by PACT at distance and near and reduction of more than 10 PD from largest of distance and near angles at enrollment
2. Esotropia less than 6 PD at distance and near by SPCT
3. No decrease in Preschool Randot stereoacuity of 2 or more octaves from the enrollment stereoacuity and no drop to nil
4. No reoperation or treatment with botulinum toxin
5. No non-surgical treatment for IXT during the study

Indeterminate = ALL of the following criteria are met at the 3-year visit:

1. Patient meets one or more of the following:

- Exophoria >=10PD by PACT at distance or near
- Exodeviation less than 10PD by PACT at distance and near but no reduction of more than 10 PD from largest of distance and near angles at enrollment
- Intermittent esotropia or esophoria >=6PD at distance and/or near

2. No decrease in Preschool Randot stereoacuity of 2 or more octaves from the enrollment stereoacuity or a drop to nil
3. No reoperation or treatment with botulinum toxin

6.2 Secondary Data Analysis

All secondary analyses will be conducted on the primary cohort and stratified by IXT type.

6.2.1 Subgroup Analyses

A secondary analysis will assess whether the treatment group difference in the proportion of patients with surgical failure by 3 years varies in subgroups based on baseline factors. Interpretation of subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group difference. Subgroup analyses will be interpreted with caution, particularly in the absence of an overall treatment group difference.

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

The general approach for subgroup analyses will be to determine the proportion of patients with surgical failure for each treatment group within each subgroup, using the same method as for the primary analysis. Factors showing evidence of interaction with treatment effect will be formally assessed by including an interaction term in a Cox proportional hazards model that includes the factor. In general, power will be low for formally detecting interactions unless the interaction is very large.

6.2.2 Surgical Failure Proportion at 3 Year Timepoint

The binomial proportion of patients who meet surgical failure criteria *at* the 3 year visit (as opposed to *by* the 3 year visit) will be estimated for each treatment group and compared using Fisher's exact test.

Patients who do not return for the 3 year visit will not be included in the analysis, including patients who met surgical failure criteria at an intermediate visit. Patients who complete the visit will be classified based on their status at 3 years, regardless of whether they met surgical failure criteria at an earlier timepoint, unless they have been re-operated (or treated with botulinum toxin), in which case they will be classified as a surgical failure.

The potential for bias in the treatment group comparison is recognized. Once a patient has met the clinical criteria for surgical failure criteria at an interim follow up visit, the decision to reoperate—and thus permanently classify the patient as a surgical failure for the analysis *at* 3

years—is at the discretion of an unmasked investigator and therefore could be related to treatment group. To assist in assessing for potential bias, the extent to which treatment group is related to the decision to reoperate will be evaluated.

6.2.3 Success Proportion at 3 Year Timepoint

The estimated proportion of patients who meet criteria for 'success' at the 3-year outcome exam (section 6.1.1) will be calculated and compared between treatment groups using a Fisher's exact test. A 95% confidence interval on the difference of proportions between the two groups also will be calculated.

The potential for bias in this treatment group comparison is recognized. Once a patient has met the clinical criteria for surgical failure criteria at an interim follow up visit, the decision to reoperate—and thus prevent the patient from being classified as a success for the 3 year analysis—is at the discretion of an unmasked investigator and therefore could be related to treatment group. To assist in assessing for potential bias, the extent to which treatment group is related to the decision to reoperate will be evaluated.

6.2.4 Analysis of Secondary Outcomes

Additional secondary analyses will be performed to assess whether treatment group differences exist for secondary outcomes: near stereoacuity, distance stereoacuity, monofixation status as determined using Titmus stereoacuity data, monofixation status determined as using Preschool Randot stereoacuity data, development of amblyopia, and quality of life.

6.3 Exploratory Analyses

6.3.1 Exploratory Analyses in Primary Cohort

Exploratory analyses will be stratified by IXT type and conducted in the primary cohort (i.e. patients whose largest angle by PACT at enrollment is between 15 and 40 PD inclusive).

As exploratory analyses, the primary analysis comparing failure proportions by 3 years (section 6.1), the comparison of failure proportions at 3 years (6.2.2) the comparison of success proportions at 3 years (6.2.3) will be repeated using the same outcome classification of surgical failure, success, or indeterminate as described section 6.1.1., with the following exception:

- At the 3-year visit, for patients who are currently prescribed prism and/or deliberate overminus: the Preschool Randot at near score to be used for the outcome classification will be the one tested *without* wearing prism or overminus. If this measurement shows a decrease of at least 2 octaves (at least 0.6 log arcsec) from the enrollment measurement, or to nil, to avoid adding to testing burden and to the complexity of visits, a confirmatory retest *is not* needed to be considered a surgical failure for this analysis.

6.3.2 Exploratory Analyses in Patients with Baseline Angle > 40 to 50 PD

Additional exploratory analyses will be stratified by IXT type and conducted in a secondary cohort of patients whose largest angle by PACT at enrollment is > 40 to 50 PD.

The proportion of patients with surgical failure by 3 years will be calculated and will be compared between treatment groups using the same method as for the primary analysis.

6.4 Safety Analyses

Postoperative complications will be tabulated according to treatment group.

6.5 Additional Tabulations and Analyses

The following will be tabulated according to treatment group:

1. Baseline demographic and clinical characteristics
2. Baseline data for study completers vs. non-completers
3. Protocol deviations

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

6.6 Interim Analysis

There are no plans to formally assess surgical failure at a timepoint earlier than 3 years because it is the long-term outcome that is of clinical interest and because the treatment groups are expected to differ in the timing of surgical failure and in the criteria met for surgical failure. Patients receiving unilateral lateral rectus recession with medial rectus resection (R&R) are expected to fail earlier, due primarily to consecutive esotropia (i.e., overcorrection) which cannot be managed with prism, whereas patients receiving bilateral lateral rectus recessions (BLRrec) are expected to have better short-term motor outcomes but fail later, due primarily to recurrence of the intermittent exotropia over the long term. A treatment group comparison of failure proportions at a timepoint before 3 years would therefore be expected to be biased against R&R.

An interim analysis of partial 3-year data is not planned because by the time 50% of the cohort has 3-year data, recruitment will have ended and all patients will have had surgery.

6.7 Sample Size Estimation

The study is powered for an appropriate number of patients of each IXT type in the primary cohort.

Table 4 shows the estimated number of patients needed per group to detect specific differences in the proportion of patients meeting surgical failure criteria by 3 years (*section 6.1.1*) with power of 0.90 and type I error rate of 0.05 using the Fisher's exact test:

Table 4: Sample size needed per group to detect the tabled difference in proportion of failure with type I error=5% and power=90%

Proportion of failure for bilateral lateral recessions	**Proportion of failure for unilateral lateral rectus recessions with medial rectus resections**				
	0.35	0.30	0.25	0.20	0.15
0.50	240	135	**85**	58	41
0.45	523	231	128	80	53
0.40	2008	496	216	118	72
0.35	--	1182	459	197	105
0.30	1882	--	1713	411	173

Based upon estimates in the literature for basic type IXT, the difference in failure proportion between bilateral lateral recessions (BLRrec) and unilateral lateral rectus recessions with medial rectus resections (R&R) for the treatment of IXT ranges from as little as 4% (failure rates of 44% vs. 40% respectively)[13] to as much as 30% (failure rates of 48% vs. 18% respectively).[12] It was felt clinically meaningful to power the study to detect a difference between treatment groups only if the true difference was at least 25%, assuming a failure rate of 25% in the BLRrec group and 50% in the R&R group, respectively). In the absence of literature comparing surgical outcomes in patients with pseudo divergence excess type IXT, the analysis for these patients will be powered similarly to the analysis for basic type IXT patients.

Given estimated failure proportions of 50% with BLRrec and 25% with R&R, and accounting for 10% loss to follow-up prior to repeat operation, 378 patients will need to be enrolled in the primary cohort (189 with basic type IXT and 189 with pseudo divergence excess type IXT), half of whom will be randomized to each treatment group.

An additional 76 patients whose largest exodeviation by PACT at enrollment is > 40 to 50 PD (38 with basic type IXT and 38 with pseudo divergence excess type IXT) are expected to be enrolled as a secondary cohort during recruitment for the primary cohort. Recruitment for the secondary cohort will be monitored during recruitment of the primary cohort. If a secondary cohort is enrolling fewer patients than expected, recruitment for the secondary cohort could be terminated before recruitment for the primary cohort has ended.

As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects who have signed an informed consent form can be randomized up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomized subjects will be 474.

CHAPTER 7: REFERENCES

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