INTERMITTENT EXOTROPIA STUDY 3 (IXT3)

A Pilot Randomized Clinical Trial of Overminus Spectacle Therapy for Intermittent Exotropia

PROTOCOL

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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 that address management of intermittent exotropia in children.

1.1 Intermittent Exotropia

Intermittent exotropia (IXT) is the most common form of childhood-onset exotropia with an incidence of 32.1 per 100,000 in children under 19 years of age.[1] The onset of IXT is thought to often occur in the first year of life.[2] Among children 1 to 2.5 years of age, IXT has been estimated to occur in 245 children per 100,000.[3] IXT is characterized by an exotropia that is not constant and is mainly present in the distance but may also be present at near.

Treatment for IXT may be either non-surgical or surgical.[4] While surgery is often considered for treatment of IXT, many cases of IXT are treated using non-surgical interventions,[5, 6] such as overminus lenses or occlusion.[7]

1.2 Overminus Lens Therapy

Overminus lens therapy involves prescription of additional minus power in the spectacle lenses and the spectacles are worn full-time.

Overminus lens therapy for exodeviations was described as early as 1913 by Landolt.[8] In a survey of American and Canadian pediatric ophthalmologists,[9] 52% reported that they routinely used some form of non-surgical therapy in the management of childhood IXT, with 34% of the 52% using overminus lenses. When the same survey was administered to members of the International Strabismological Association, half of the respondents said they used overminus lenses to treat childhood IXT.[10]

1.3 Possible Mechanisms of Overminus Lens Therapy

Overminus lens therapy for IXT is thought to work by stimulating accommodative convergence, therefore reducing the angle of exodeviation and allowing fusion,[11] or by clearing distance blur (caused by excessive compensatory accommodative convergence) and thus allowing fusion.[5] An alternative hypothesis is that fusional convergence often induces convergence accommodation that results in distance blur, but this induced blur is mitigated by minus lenses allowing the better control of the IXT without blur.[12] Regardless of the mechanism, overminus lens therapy may reduce the angle of the exodeviation, or increase the control of the exodeviation (reducing the amount of time the exodeviation is manifest), or both.

1.4 Short-term and Long-term Rationale for Using Overminus Lens Therapy

There appear to be two main reasons for implementing overminus lens treatment in IXT:

1) As a temporizing measure to reduce the angle of the exodeviation, or increase the control of the exodeviation, or both, for example in a child considered too young for surgery or ocular motor training exercises.
2) As a long-term strategy, to treat the IXT by improving control of the exodeviation, with eventual weaning of the overminus to a point at which the subject is well compensated in his or her regular refractive correction.

1.5 Public Health Importance of Proposed Randomized Clinical Trial

Although overminus lens treatment for IXT is widely used in clinical care, there have been no RCTs evaluating its effectiveness. Understanding the effectiveness of overminus lens treatment for IXT has important public health implications because successful treatment may reduce the proportion of children needing to undergo surgery. Conversely, evidence of poor treatment effectiveness with overminus lens therapy would prevent children from undergoing unnecessary treatment with overminus lenses.

1.6 Previous Studies of Overminus Lens Therapy

Previous studies of overminus lens therapy have been limited to small case series, most with poorly defined methods of prescribing overminus, variable amounts of overminus prescribed, and poorly defined definitions of success (Table 1).

Table 1. Previous studies of overminus lens treatment for IXT

Author, year	Subject population	Method of over-minus determination	Results	Comment
Kennedy 1954[13]	N=103 successfully treated subjects (failures excluded)	Multiple tests of accommodation performed (described in detail by author). "Final lens selected is arrived at in light of all the data yielded by the various tests outlined, and is usually the lowest powered concave lens which produces objective orthophoria." Power may subsequently be changed.	Report only included successful subjects	Success defined as presence of one of the following: "cosmetically straight," "some fusion," or "constant fusion." Treatment duration not reported
Caltrider 1983[14]	N=35 N=10/35 seen 1 year after discontinuing overminus	Prescribed between 2.00D and 4.00D overminus. No other details provided.	46% qualitative improvement in overminus; 7/10 maintained improvement out of overminus	Qualitative improvement defined as neither parents nor physician noticing manifest exodeviation when wearing overminus. Treatment duration from 2 to 156 months

Author, year	Subject population	Method of over-minus determination	Results	Comment
Goodacre 1985[15]	N=34 aged 1 to 6 years	All prescribed 3.00D overminus initially. Amount of minus increased at follow-up if necessary to further improve control (up to a max of 5.00D overminus). No other details provided.	62% "cured"	Cure defined as exophoria near, distance, and far distance when wearing overminus lenses. Treatment duration at least 12 months
Rutstein 1989[16]	N=40 aged 1 to 15 years	Amount of overminus prescribed ranged from 0.50D to 3.75D. No other details provided.	Outcomes not described in terms of overminus success	Main outcome measure was change in refractive error (after wearing overminus). No treatment outcomes reported
Donaldson 1991[17]	N=18 aged 2 to 17 years	"Children of normal retinoscopy were generally ordered 2.00D, 2.50D or 3.00D overminus depending on the ophthalmologist's assessment of expected tolerance."	72% success	Success defined as binocular single vision for all distances & symptoms relieved when wearing overminus lenses. Treatment duration at least 6 months.
Reynolds 1994[11]	N=74 aged 14 months to 13 years	Prescribed 1.00D to 2.50D overminus: the initial amount was "varied according to baseline refractive error and age of subject." No other details provided.	62% success	Success defined as conversion to orthophoria, pure exophoria, or IXT <10pd. Treatment duration at least 3 to 6 months
Kushner 1999[18]	N=74 mean age 4 years	Prescribed overminus spectacles "if seem beneficial in controlling deviation". For myopic refractions: additional 1.00D to 2.00D overminus. For hyperopic refractions: additional minus until final SE between -1.00D and -2.00D. *In addition 4 to 6 BI also incorporated sometimes.* If satisfactory control not seen at first follow-up exam, added patching for anti-suppression	19% "improved control" without overminus correction 46% still in overminus 5 years later	Outcomes regarding effectiveness of overminus not clearly reported (study primarily on whether overminus causes myopia). Treatment duration from 6 to 156 months.

196

Author, year	Subject population	Method of over-minus determination	Results	Comment
Watts 2005[19]	N=24 aged 2-17 years	Prescribed "maximum tolerated minus": minimum 2.00D to maximum 4.00D depending on ability to read 20/20 and N5 with overminus in place. Hyperopic subjects - Rx reduced by minimum of 2.00D, max 4.00D.	71%	Success defined as improved control (reduction in Newcastle control score) when wearing overminus. Treatment duration 3 months.
Rowe 2009[20]	N=21 aged 1-9 years, Newcastle control score of 3 or worse	Prescribed minimum minus to reduce angle and achieve control of the manifest deviation at near & dist. Started with 1.00D and increased by 0.50D increments until control was achieved. Actual over-minus initially prescribed: median 2.00D; range 1.00D to 3.00D.	24% success (out of overminus)	Success defined as exophoria at near, distance, and far distance, with binocular control at all distances OUT of overminus spectacles at 5 years follow-up. Treatment duration from 6 to 62 months in overminus and from 6 to 39 months out of overminus.

1.7 Methods of Prescribing Overminus

As illustrated in Table 1 above, the amount of overminus prescribed in previous studies varied from 0.50D to 4.00D, and also differed by the preference for one of 4 philosophical approaches for prescribing overminus:

1) a fixed amount of overminus, regardless of cycloplegic refractive error
2) a fixed amount of overminus over and above cycloplegic refractive error, to achieve a specific amount of accommodative demand
3) a customized approach, tailoring the amount of overminus to a response during a single office examination, either in improved control or improved angle of distance exotropia
4) a customized approach, tailoring the amount of overminus to a response over successive office visits in improved control or improved angle of distance exotropia

1.8 Customized Method of Prescribing Overminus

Although a customized approach to prescribing overminus is sometimes used in clinical practice, there are significant obstacles to incorporating such an approach into a rigorous clinical study. The measures used to assess response to overminus are intrinsically variable. Most practitioners use “control” (the proportion of time that the deviation is manifest) to judge response, but although control can be quantified more rigorously in the office using an office control score,[21] a single control score has been found to be highly variable.[22] Adequate representation of control

can better be achieved by measuring control at least three times during an office exam and calculating a mean value.[23]

Members of the Planning Committee for this study piloted the assessment of control through several steps of increasing or decreasing the overminus lens power to determine a power that better controls the IXT, in a single office examination. We found this method far too time consuming and unworkable for the proposed RCT even when assessing response to each level of overminus with a single measure of control.

In summary, it would be very challenging to protocolize a method for customized prescribing of overminus using established methods for assessing control.

1.9 Fixed Method of Prescribing Overminus

Whereas some clinicians prescribe a fixed overminus spectacle correction regardless of the cycloplegic refraction (e.g., -1.50D spectacles for a patient with plano and for a patient with +0.50D hyperopia), others prescribe a predetermined amount of overminus by adding the minus power to the cycloplegic refraction e.g., adding -1.50D overminus for all subjects, they would prescribe -1.50D spectacles for plano and -1.00D spectacles for +0.50D hyperopia.

Polling the PEDIG Investigator group at the recent Investigator meeting (Feb. 7, 2014) revealed that the vast majority (>95%) would prefer a prescribing approach that standardized the amount of induced accommodation, achieved by adding a fixed amount of overminus to the cycloplegic refraction. This method reflects the commonly held belief that the treatment mechanism of overminus is related to induced accommodation.

1.10 Determining Dose of Overminus for Current Study

In the IXT2 study (patching versus observation) we found that a large proportion of 3- to 7-year-old children (the target age range for this overminus study) presented with low levels of hyperopia. Nearly all such children were not wearing spectacles because they were able to accommodate well and did not need the hyperopic correction for excellent visual acuity. If we are to include children with hyperopia in a study of overminus lenses, we can only include low levels of hyperopia if we want to prescribe a reasonable level of overminus. Otherwise we would create untenable situations, such as including a subject with +2.00D hyperopia, prescribing 2.50D overminus, writing a spectacle prescription for -0.50D sphere, and calling this prescription “overminus” treatment.

The consensus of the Planning Committee, affirmed by the Investigator Group at the February 2014 Study Group meeting, was that a final spectacle prescription of -1.50D should be the lowest level of overminus spectacles prescribed and still be considered “overminus.” There was also a consensus that children with up to +1.00D SE hyperopia should be included, since low levels of hyperopia are common in children with IXT.

Levels of overminus greater than 2.50D were of concern to many of the PEDIG Investigators. For example, overminus of 4.00D was felt to be unreasonable, requiring accommodation of 4.00D at distance fixation and 7.00D for near activities and reading.

The most reasonable dose of overminus was therefore felt to be -2.50D over the cycloplegic refraction.

1.11 Possible Study Questions Related to Overminus Lens Therapy

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

1. Does overminus lens therapy have an initial short-term therapeutic effect for IXT while wearing overminus spectacles (over a number of weeks)?
2. Does overminus lens therapy have a long-term therapeutic effect for IXT while wearing overminus spectacles (over many months or years)?
3. Does overminus lens therapy have a long-term therapeutic effect for IXT when overminus spectacles are discontinued?
4. What magnitude of overminus lens therapy is most successful for treating IXT, e.g., achieving the desired therapeutic effect without inducing adverse symptoms?

In the initial planning stages of the study we considered a full-scale RCT might be needed to address the first three questions, likely comparing overminus therapy to control spectacles, and so the Planning Committee initially focused on the question of overminus lens power as one that might need to be addressed in a preliminary pilot RCT. The initial plan was to collect data on a preliminary estimate of response, compliance, acceptability, and side effects with each of two treatment regimens: 2.00D of overminus and 3.00D of overminus (starting with the child's cycloplegic refraction). The aim was to use such data to choose an overminus lens power to advance to a full-scale RCT, comparing that treatment to control.

On further discussion, it became apparent that it would be difficult to use the data from such a pilot to choose one of the treatments for the subsequent study, unless there was a very large difference in treatment effectiveness or large differences in side effect profiles.

In contrast, a pilot RCT of overminus versus control would be useful to establish preliminary estimates of treatment effect both in a treatment group and in a control group, particularly if a new outcome measure could be incorporated (the triple control score). For such a pilot RCT, a single dose of overminus needs to be selected, and from the foregoing discussion, a dose of 2.50D overminus based on the cycloplegic refraction, in children with IXT who have no more than +1.00D SE hyperopia, seems to be the most reasonable option.

1.12 Definitions of Treatment Response

Previous studies have differed in their definitions of treatment response, including reduction of the magnitude of exodeviation,[14 11, 24] improved control,[20] or both combined with good stereoacuity and good cosmesis assessed by parental impression.[24] Some studies report outcomes while the subject is still in overminus lens treatment,[19] some post-treatment,[14, 20] and for others, treatment status at outcome is unclear.[11, 13, 24]

Because the initial purpose of the treatment of IXT with overminus spectacles is to better align the eyes for a greater proportion of the time, and single binocular vision with high grade stereoacuity is only associated with good ocular alignment, it would seem reasonable to primarily focus on "control" of the distance deviation as the first step in evaluating effectiveness of overminus lens treatment. Due to the variability of single measures of control, we propose using the recently described "triple control score,"[23] a mean of 3 measures obtained at various times during a 20- to 40-minute office examination.

Treatment effect will be assessed in our study by analyzing the change in mean control score from baseline to outcome examination (primary analysis) and by comparing the proportion of subjects with "treatment response" (secondary analysis).

Data simulations were used to estimate the amount of change in control expected from test-retest variability (including short term variability of the condition) and to evaluate the risk of misclassification using various thresholds for defining treatment response. A set of 10,000 stable subjects each with a mean control score (average of 3 measurements) of 2 or worse was simulated using 1) the distribution of baseline distance control scores from subjects 3 to <11 years of age in the IXT2 study who would be eligible for the present study to estimate initial control scores, and 2) actual test-retest data collected on 336 test-retest pairs from 158 subjects at the Mayo Clinic to estimate the probability that a subsequent score would be a certain value (e.g., probability that a control score of five would subsequently test a three). Based on the simulated data, the mean difference in control expected from test-retest variability was estimated at -0.058 points with a standard deviation of 0.926 points. The simulations-estimated 95% limits of agreement of 1.82 points indicated that for a given subject, a 2-point change in the mean control score would be required to have reasonable certainty of exceeding test–retest variability. Using a 2-point threshold, the simulations yielded a misclassification rate for improvement of 2% assuming no real change has occurred. Nevertheless, defining response as a 2-point change was ultimately not felt to be feasible given that the target population in which overminus lenses are often used includes subjects with control scores as low as 2 points (no exotropia unless dissociated, recovers in > 5 seconds) and that it was felt very unlikely that a large proportion of such subjects could improve to a score of 0 (pure phoria). Consequently, the Planning Committee consensus was that a clinically meaningful "response" would be defined as an improvement of at least 1 point on the mean control score. For a 1-point threshold, the simulations yielded a misclassification rate for improved versus not improved of 18% assuming no real change has occurred. Therefore, in the proposed RCT, the control group response rate would be estimated to be 18% (rounded to 20%) assuming no real change occurs. As a result, it is acknowledged that the response rate will be somewhat overestimated in both treatment groups.

1.13 Timing of Outcome Intervention for Current Study

For the pilot RCT to evaluate initial response to overminus spectacles, a short "several-week" study is proposed. If a reasonable initial response without significant adverse effect is found, a subsequent full-scale RCT would evaluate the long-term effectiveness of overminus lenses (for example, over 1 year) and then evaluate the subsequent effectiveness of maintaining control after the overminus lens treatment has been discontinued (for example, 6 months after return to non-overminus spectacles or no spectacles).

1.14 Study Objective

The objective of this short-term, pilot randomized trial comparing 2.50D overminus lens treatment vs. non-overminus (spectacles without overminus or no spectacles) is to determine whether to proceed to a full-scale, longer-term randomized trial. This decision will be based primarily on assessing the initial (8-week) response to overminus by comparing treatment groups on the following outcomes:

- Mean distance IXT control score (each patient's score is the mean of 3 control scores) (primary outcome)
- The proportion of subjects with treatment response, defined as 1 or more points improvement in mean of 3 distance IXT control scores (secondary outcome)

- Adverse effects, near visual acuity outcomes, and spectacle wear compliance

1.15 Synopsis of Study Design

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

- Age 3 to < 7 years
- Intermittent exotropia (manifest deviation) meeting all of the following criteria:
    - Intermittent exotropia or constant exotropia at distance
        - Mean distance control score of 2 points or more (mean of 3 assessments over the exam)
    - Intermittent exotropia, exophoria, or orthophoria at near
        - Control score ≤ 4 on at least 1 of 3 near assessments of control (cannot have a score of 5 points on all 3)
    - Exodeviation at least 15Δ at distance measured by prism and alternate cover test (PACT)
    - Near deviation does not exceed distance deviation by more than 10Δ by PACT (convergence insufficiency type IXT excluded)
- No previous non-surgical treatment for IXT (other than refractive correction), including vision therapy for IXT, within the past 6 months.
- No vision therapy, patching, atropine, or other penalization for amblyopia during the last 2 weeks
- No prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- No previous substantial overminus treatment, defined as wearing spectacles that are overminused by 1.00D SE or more (treatment with lenses overminused by less than 1.00D SE is allowed at any time prior to enrollment).
- Spherical equivalent in both eyes between -6.00D and +1.00D inclusive
- Distance visual acuity 0.3 logMAR (20/40) or better (by ATS-HOTV) in both eyes
- No interocular difference of distance visual acuity more than 0.2 logMAR (2 lines)
- Child must be wearing refractive correction (pre-study spectacles) for at least 1 week if refractive error (based on cycloplegic refraction performed within 7 months) meets specific criteria (*see section 2.2*) and these spectacles must be within specific pre-randomization tolerances (*see section 2.2*)

Sample size

54 children (27 per treatment group)

Treatment

Randomization (1:1) to the following groups:

- Overminus: 2.50D overminus spectacles
- Non-overminus: spectacles without overminus or no spectacles

Visit Schedule

- Enrollment Exam
- Outcome Exam: 8 weeks ± 2 weeks after randomization

Testing Procedures

Distance and near control of IXT (3 measurements) and distance and near PACT will be measured by a study-qualified examiner at enrollment, but by a Masked Examiner at 8 weeks. Near stereoacuity, distance visual acuity, and binocular near visual acuity will be measured by a study-qualified examiner at both visits. In addition, symptoms of headache, eye strain, and problems with spectacle wear will be assessed at both visits.

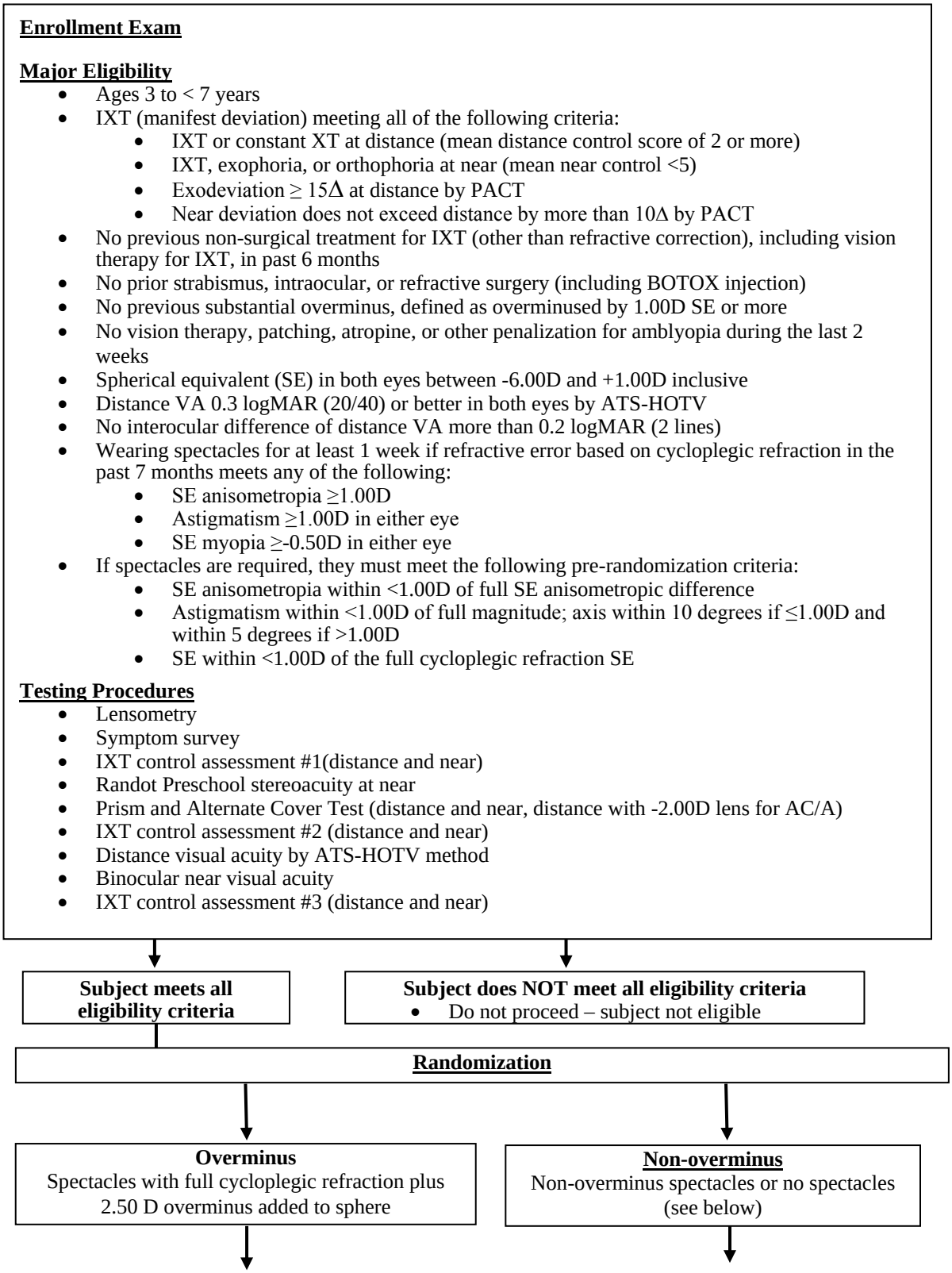
Primary Analysis

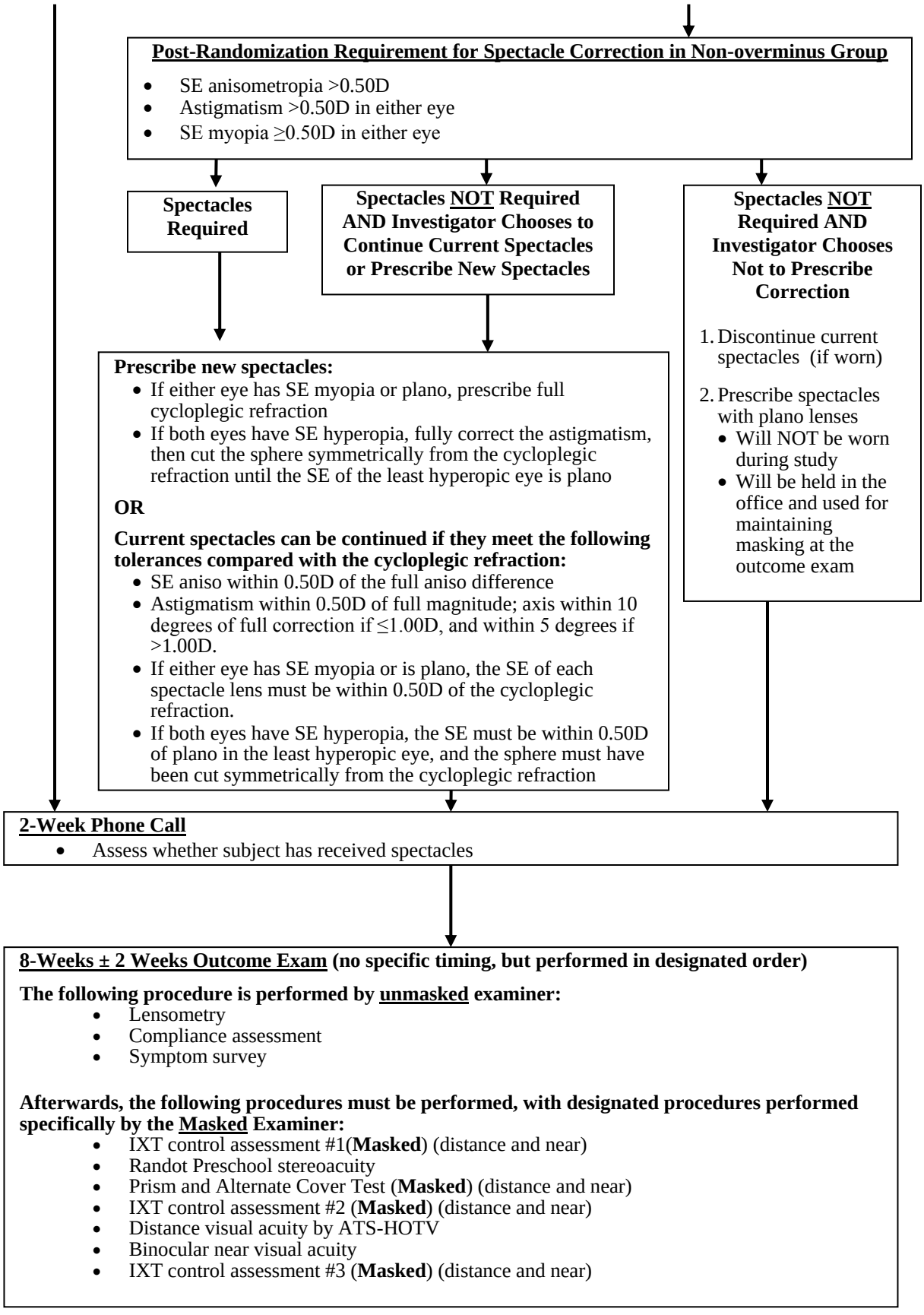
- A comparison of mean distance control scores (mean of the 3 assessments over the exam) between the 2.50D overminus group and the non-overminus group (spectacles without overminus or no spectacles) at 8 weeks.

Secondary Analysis

- A comparison of the proportion of subjects showing a "treatment response," defined as an improvement of at least 1 point in distance control (mean of the 3 assessments over the exam) between enrollment and 8 weeks.

1.16 Study Flow Chart




Post-Randomization Requirement for Spectacle Correction in Non-overminus Group
SE anisometropia >0.50D
Astigmatism >0.50D in either eye
SE myopia ≥0.50D in either eye
Spectacles Required
Spectacles NOT Required AND Investigator Chooses to Continue Current Spectacles or Prescribe New Spectacles
Spectacles NOT Required AND Investigator Chooses Not to Prescribe Correction
1. Discontinue current spectacles (if worn)
2. Prescribe spectacles with plano lenses
Will NOT be worn during study
Will be held in the office and used for maintaining masking at the outcome exam
Prescribe new spectacles:
If either eye has SE myopia or plano, prescribe full cycloplegic refraction
If both eyes have SE hyperopia, fully correct the astigmatism, then cut the sphere symmetrically from the cycloplegic refraction until the SE of the least hyperopic eye is plano
OR
Current spectacles can be continued if they meet the following tolerances compared with the cycloplegic refraction:
SE aniso within 0.50D of the full aniso difference
Astigmatism within 0.50D of full magnitude; axis within 10 degrees of full correction if ≤1.00D, and within 5 degrees if >1.00D.
If either eye has SE myopia or is plano, the SE of each spectacle lens must be within 0.50D of the cycloplegic refraction.
If both eyes have SE hyperopia, the SE must be within 0.50D of plano in the least hyperopic eye, and the sphere must have been cut symmetrically from the cycloplegic refraction
2-Week Phone Call
Assess whether subject has received spectacles
8-Weeks ± 2 Weeks Outcome Exam (no specific timing, but performed in designated order)
The following procedure is performed by unmasked examiner:
Lensometry
Compliance assessment
Symptom survey
Afterwards, the following procedures must be performed, with designated procedures performed specifically by the Masked Examiner:
IXT control assessment #1(Masked) (distance and near)
Randot Preschool stereoacuity
Prism and Alternate Cover Test (Masked) (distance and near)
IXT control assessment #2 (Masked) (distance and near)
Distance visual acuity by ATS-HOTV
Binocular near visual acuity
IXT control assessment #3 (Masked) (distance and near)

427

CHAPTER 2: ENROLLMENT AND RANDOMIZATION

2.1 Eligibility Assessment and Informed Consent

The study will enroll 54 subjects aged 3 to < 7 years with IXT who meet eligibility criteria. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Subjects whose parents have signed an informed consent form can be randomly assigned to treatment up until the end date, which means the expected recruitment might be exceeded. The maximum number of randomly assigned subjects will be 60.

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

2.2 Eligibility Criteria

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

- Age 3 years to < 7 years
- Intermittent exotropia (manifest deviation) meeting all of the following criteria:
  - Intermittent exotropia or constant exotropia at distance
    - Mean distance control score of 2 points or more (mean of 3 assessments over the exam)
  - Intermittent exotropia, exophoria, or orthophoria at near
    - Subject cannot have a score of 5 points on all 3 near assessments of control
  - Exodeviation at least 15Δ at distance measured by PACT
  - Near deviation does not exceed distance deviation by more than 10Δ by PACT (convergence insufficiency type IXT excluded)
- No previous non-surgical treatment for IXT (other than refractive correction), including vision therapy for IXT, within the past 6 months.
- No previous substantial overminus treatment, defined as wearing spectacles that are overminused by 1.00D SE or more (treatment with lenses overminused by less than 1.00D SE is allowed at any time prior to enrollment).
- No vision therapy, patching, atropine, or other penalization for amblyopia during the last 2 weeks
- No prior strabismus, intraocular, or refractive surgery (including BOTOX injection)
- Cycloplegic refraction within 7 months, but NOT on the day of enrollment
- Spherical equivalent (SE) in both eyes between -6.00D and +1.00D inclusive
- Distance visual acuity 0.3 logMAR (20/40) or better (by ATS-HOTV) in both eyes
- No interocular difference of distance visual acuity more than 0.2 logMAR (2 lines)
- Child must be wearing refractive correction (pre-study spectacles) for at least 1 week if refractive error (based on cycloplegic refraction performed within 7 months) meets any of the following:
  - SE anisometropia ≥1.00 D
  - Astigmatism ≥1.00 D in either eye
  - SE myopia ≥-0.50 D in either eye

  Refractive correction must meet the following criteria relative to the cycloplegic refraction:

- SE anisometropia must be within <1.0D of the SE anisometropic difference
- Astigmatism must be within <1.00D of full magnitude; axis must be within 10 degrees if ≤1.00D, and within 5 degrees if >1.00D.
- The SE of the spectacles must be within <1.00D of the full cycloplegic refraction SE.
  - A correction that yields at least 1.00 D *more minus* SE than the cycloplegic refraction SE is considered previous substantial overminus lens treatment and the patient is not eligible.

- No current contact lens wear
- No abnormality of the cornea, lens, or central retina
- Gestational age ≥ 32 weeks
- Birth weight > 1500 grams
- No Down syndrome or cerebral palsy
- No severe developmental delay which would interfere with treatment or evaluation (in the opinion of the investigator). Subjects with mild speech delays or reading and/or learning disabilities are not excluded.
- No disease known to affect accommodation, vergence, and ocular motility such as multiple sclerosis, Graves orbitopathy, myasthenia gravis, diabetes mellitus, or Parkinson disease
- No current use of any ocular or systemic medication known to affect accommodation or vergence, such as anti-anxiety agents (e.g., Librium or Valium), anti-arrhythmic agents (e.g., Cifenline, Cibenzoline), anti-cholinergics (e.g., motion sickness patch (scopolamine)), bladder spasmolytic drugs (e.g., Propiverine), hydroxychloroquine, chloroquine, phenothiazines (e.g., Compazine, Mellaril, Thorazine), tricyclic antidepressants (e.g., Elavil, Nortriptyline, Tofranil)
- Parent understands the protocol and is willing to accept randomization to overminus spectacles or non-overminus status
- Parent has home phone (or access to phone) and is willing to be contacted by Jaeb Center staff and Investigator's site staff
- Relocation outside of area of an active PEDIG site within next 8 weeks is not anticipated

2.3 Historical Information

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

2.4 Testing at the Enrollment Exam

Initial testing at the Enrollment Exam will be with the subject wearing "habitual correction" (with spectacles if spectacles are currently being worn or without spectacles if not wearing spectacles).*

* The exception is that a subject who does not require spectacles but is wearing a pair of spectacles that does not meet pre-randomization spectacle tolerances (*see section 2.2*) can have enrollment testing performed with or without these "incorrect" spectacles, provided the subject can meet the visual acuity eligibility criteria (*see section 2.2*) in the given refractive state. If visual acuity criteria are not met, the subject is not eligible at that visit.

Trial frames should NOT be used for testing at the enrollment exam for any reason.

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

1. Spectacle Prescription Verification (Lensometry): Prior to performing the enrollment examination, the subject's pre-randomization spectacle correction (if worn) is to be verified using a lensometer.
2. Symptom Survey: A brief survey of symptoms that may be associated with overminus such as headaches, eye strain, and problems with spectacle wear will be administered to the parents of the subjects. Parents are asked to respond to the survey questions based on their observations of their child in the past 2 weeks. Response options are based on frequency of observations; never, rarely, sometimes, often, always, and not applicable.
3. Control of the Exodeviation #1:
   - Assessment of control must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.

   Control of exodeviation will be assessed in the habitual correction at distance and near using a standardized IXT control scale (*see below*).[21]
   - Distance (6 meters) – fixing on an accommodative target such as a video or reading optotype letters
   - Near (1/3 meter – fixing on Lang near-viewing stick or similar accommodative target)

   The scale below applies to both distance and near separately.

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

   Directions:

   Step1: Assessment before any dissociation: Levels 5 to 3 are assessed during a 30-second period of observation; first at distance fixation and then at near fixation for another 30-second period. Both distance and near are assessed before any dissociation (i.e., before step 2, when assessing control scores of 0, 1 and 2).If the subject is spontaneously tropic (score 3, 4 or 5) at a specified test distance, then step 2 (assessment after standard dissociation) is skipped at that specific test distance.

   Step 2: Assessment with standardized dissociation: If no exotropia is observed during step 1 (i.e. the 30-second period of observation at the specified test distance), levels 2 to 0 are then assessed as the worst of 3 rapidly successive trials of dissociation:
   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 (second assessment under dissociation) and the time to re-establish fusion is similarly measured.
   3. A third assessment under dissociation is performed, covering the eye (for a 10-second period) 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. Since the level under dissociation is recorded as the worst of the three assessments, if a score of 2 (>5 seconds recovery) is noted on the first or second dissociation, then subsequent dissociation(s) are not needed.

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

4. Stereoacuity Testing: Stereoacuity will be assessed with habitual correction using the Randot Preschool stereotest at near (performed at 40 cm). A specific level of stereoacuity is not required for eligibility.
5. PACT Testing & AC/A Determination:
   - PACT testing must be performed by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist.
   - PACT will be assessed in primary gaze and without cycloplegia as follows and using procedures outlined in the IXT Testing Procedures Manual.
   - At distance (6 meters) and near (1/3 m) in habitual correction
   - AC/A assessment at distance (6 meters) measuring the PACT with the subject wearing -2.00D lenses over his/her habitual correction. The AC/A ratio is calculated by taking the difference between the distance PACT measurements with and without -2.00D lenses and dividing the difference by 2.
6. Control of the Exodeviation #2 (repeat) (*see item #3*).
   - The same examiner should assess IXT control each of the three different times that control is assessed during the enrollment visit.
7. Distance Visual Acuity Testing: Monocular distance visual acuity testing with the habitual correction and without cycloplegia will be measured using the ATS-HOTV testing protocol on any certified visual acuity system.
8. Binocular Near Visual Acuity: Binocular near visual acuity will be tested in habitual correction using the ATS4 near visual acuity test.
9. Control of the Exodeviation #3 (repeat) (*see item #3*)
   - The same examiner should assess control each of the three different times that control is assessed during the enrollment visit.
10. Additional Clinical Testing:
    - Ocular examination as per investigator's clinical routine to rule out ocular abnormality or lens opacity (if not performed within 7 months)

2.5 Randomization

Randomization will occur at the conclusion of the Enrollment Exam after confirming that the subject meets the eligibility criteria.

Subjects enrolled in the study will be randomly assigned with equal probability to one of the following groups:

- Overminus
- Non-overminus (non-overminus spectacles or no spectacles)

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

Based on the randomized treatment group and the spectacle correction the subject is currently wearing, the study webpage will instruct the site regarding allowable prescription(s).

2.5.1 Treatment for Overminus Group

Subjects randomly assigned to the overminus group will be prescribed spectacles with -2.50D added to the sphere power of the full cycloplegic refraction. Overminus spectacles must be worn all waking hours. No IXT treatment other than overminus refractive correction can be prescribed.

2.5.2 Treatment for Non-overminus Group

Subjects in the non-overminus group will be prescribed spectacles or no spectacles, depending on whether their cycloplegic refractive error meets the minimum requirements for correction (*see section 2.5.2.1 below*) or, if the cycloplegic refractive error does not meet these requirements, whether the investigator elects to correct this minimal amount of refractive error. No IXT treatment other than refractive correction (if applicable) can be prescribed.

2.5.2.1 Post-Randomization Criteria for Refractive Error Requiring Correction

Non-overminus group subjects meeting the following refractive error criteria are required to be prescribed spectacles following randomization.

- SE anisometropia >0.50D
- Astigmatism >0.50D in either eye
- SE myopia ≥-0.50D in either eye

Note that some subjects who were not required to wear spectacles for enrollment testing may require spectacles to be prescribed post-randomization.

2.5.2.2 Non-overminus Group Subjects Requiring Refractive Correction

Non-overminus group patients requiring refractive correction must wear spectacles all waking hours.

One of the following two options must be elected:

1. Prescribe new spectacles
   - If new spectacles are being prescribed:
     - If either eye has SE myopia or is plano, prescribe full cycloplegic refraction
     - If both eyes have SE hyperopia, fully correct the astigmatism, then cut the sphere symmetrically from the cycloplegic refraction until the SE of the least hyperopic eye is plano

2. Continue current spectacles
   - Subjects already wearing spectacles may elect to continue to wear their current spectacles if the following post-randomization spectacle tolerances are met:

     Post-Randomization Spectacle Tolerance for Non-Overminus Group
     Relative to the cycloplegic refraction:
     - SE anisometropia must be within 0.50D of the SE anisometropic difference.
     - Astigmatism must be within 0.50D of full magnitude; axis must be within 10 degrees if ≤ 1.00D, and within 5 degrees if >1.00D.
     - If either eye has SE myopia or is plano, the SE of each spectacle lens must be within 0.50D of the cycloplegic refraction.
     - If both eyes have SE hyperopia, the SE must be within 0.50 D of plano in the least hyperopic eye, and the sphere must have been cut symmetrically from the cycloplegic refraction.

     Note that some spectacles worn for enrollment testing (i.e., meet the pre-randomization spectacle tolerances) may or may not meet the post-randomization tolerances.

2.5.2.3 Non-overminus Group Subjects Not Requiring Refractive Correction

Non-overminus group patients with minimal amounts of refractive error that do not meet the spectacle requirements in *section 2.5.2.1* (above) may be prescribed refractive correction at investigator discretion.

One of the following three options must be elected:

1. Prescribe no correction
   - If no refractive correction is to be prescribed (subjects with no refractive error and subjects with minimal refractive error that the investigator has not elected to correct), spectacles with plano lenses will be prescribed, to be used to preserve masking at the outcome exam. Plano spectacles are not to be worn during the study except for during the 8-week primary outcome assessment. Plano spectacles should be left at the investigator's office if dispensed at the office, otherwise the plano spectacles should be brought to the office for follow-up testing.

2. Prescribe new spectacles
   - If new spectacles are being prescribed:
     - If either eye has SE myopia or is plano, prescribe full cycloplegic refraction
     - If both eyes have SE hyperopia, fully correct the astigmatism, then cut the spheresymmetrically from the cycloplegic refraction until the SE of the least hyperopic eye is plano

3. Continue current spectacles
   - Subjects already wearing spectacles may elect to continue to wear their current spectacles if the following post-randomization spectacle tolerances are met:

     Post-Randomization Spectacle Tolerance for Non-Overminus Group
     Relative to the cycloplegic refraction:
     - SE anisometropia must be within 0.50D of the SEanisometropic difference.
     - Astigmatism must be within 0.50D of full magnitude; axis must be within 10 degrees if ≤ 1.00D, and within 5 degrees if >1.00D.
     - If either eye has SE myopia or is plano, the SE of each spectacle lens must be within 0.50D of the cycloplegic refraction.
     - If both eyes have SE hyperopia, the SE must be within 0.50 D of plano in the least hyperopic eye, and the sphere must have been cut symmetrically from the cycloplegic refraction.

     Note that some spectacles worn for enrollment testing (i.e., meet the pre-randomization spectacle tolerances) may or may not meet the post-randomization tolerances.

CHAPTER 3: FOLLOW-UP AND MANAGEMENT

3.1 Follow-up Visit Schedule

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

- Telephone call: 2 weeks 14 to 21 days to check that the spectacles have been dispensed/received and/or that the subject is wearing the new spectacles
- Outcome Visit: 8 weeks ± 2 weeks

Additional visits may be scheduled at investigator discretion.

3.2 Telephone Call

At 2 weeks following randomization, the site will contact parents to determine whether the study spectacles (overminus spectacles/non-overminus spectacles/plano spectacles) have been dispensed/received. The site will record the date that the new spectacles were received or document that they have not been received as of the call date. Parents of subjects receiving plano spectacles will be reminded that their child is not to wear the spectacles with plano lenses. If the parents have not left the plano spectacles at the site previously (at the time they were dispensed), they will be asked to bring them to the outcome exam.

3.3 Masked Examiner Testing

At the 8-week outcome visit, a Masked Examiner, who is a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist, must assess the control of the exodeviation and perform PACT testing (*see section 3.4*).

The Masked Examiner should preferably be someone *other than* the investigator. If necessary, the Masked Examiner may be the investigator if the investigator remains masked to the randomized treatment. This can be achieved by having the investigator sign the two prescriptions (one overminus prescription and one non-overminus prescription) before the coordinator proceeds with randomization, after which the coordinator would provide the parent with the prescription assigned by randomization.

The Masked Examiner must not verify the spectacles using lensometry, discuss compliance of spectacle wear with the subject or parents, or administer the symptom survey.

3.4 Outcome Visit Testing Procedures

All outcome assessments should be completed with the subject wearing his/her study spectacles (i.e., overminus spectacles, non-overminus spectacles, or plano spectacles). Someone *other than* the Masked Examiner will ensure that the subject is wearing the study spectacles (including plano spectacles if prescribed) prior to the masked exam.

- Any subjects not bringing their study spectacles to the outcome exam will be tested in trial frames. To avoid potential unmasking, the trial lenses must have wire frames (not red or black indicating minus or plus power). Care should be taken to cover any power-indicating markings with tape to ensure that masking is maintained.

The following procedures should be performed by the appropriate examiner (*see below*) and in the order specified:

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

1. Spectacle Prescription Verification (Lensometry): Prior to performing the outcome examination, the subject's spectacle correction will be verified using a lensometer (including plano lenses).
   - Spectacles should meet the following tolerances:
     - Sphere within 0.50D of prescribed
     - Cylinder within 0.50D of prescribed
     - Axis within 10 degrees of prescribed if ≤1.00D and within 5 degrees of prescribed if >1.00D
   - If spectacles do not meet these tolerances, the subject should be tested with trial frames with the intended prescription in place.
2. Compliance Assessment *(in all subjects except those prescribed plano spectacles)*: Compliance with spectacle wear since receiving the spectacles will be assessed based on discussion with the parents and using the following scale:
   - Excellent (76% to 100%)
   - Good (51% to 75%)
   - Fair (26% to 50%)
   - Poor (≤ 25%)
3. Symptom Survey: A brief written survey of symptoms associated with headaches, eye strain, and problems with spectacles wear will be administered to the parents. Parents will be asked to respond to the survey questions based on their observations of their child in the past 2 weeks. Response options are based on frequency of observations: never, rarely, sometimes, often, and always.

After the above assessments, the following procedures must be performed in the specified order. Procedures indicated as "masked" must be tested by the Masked Examiner. Procedures not indicated as "masked" may be tested by the Masked Examiner or another study-qualified examiner although it is preferred that they be completed by the Masked Examiner. All procedures should be performed with the subject wearing his/her study spectacles (or trial frames if study spectacles were left at home) and without cycloplegia:

Although testing must be performed in the specified order, there is no specified 'waiting' time that needs to occur between measurements.

4. Control of the Exodeviation #1 **(Masked):** A Masked Examiner will assess control of exodeviation at distance and near fixation using the intermittent exotropia control scale.[21]
5. Stereoacuity Testing: Stereoacuity will be assessed using the Randot Preschool stereotest at 40 cm. If the subject has no measurable stereo, this finding will be recorded as "nil".
6. PACT Testing **(Masked):** A Masked Examiner will assess PACT in primary position at distance (6 meters) and near (1/3 m) as outlined in the IXT Testing Procedures Manual.
7. Control of the Exodeviation #2 (repeat) **(Masked, *see item #4*)**
   - The same masked examiner should assess control each of the three different times that control is assessed during the visit.
8. Distance Visual Acuity Testing: Monocular distance visual acuity testing without cycloplegia will be measured using the ATS-HOTV testing protocol on a certified visual acuity system.
9. Binocular Near Visual Acuity: Binocular near visual acuity will be measured using the ATS4 near visual acuity test.

10. Control of the Exodeviation #3 (repeat) **(Masked, *see item #4)***

- The same masked examiner should assess control each of the three different times that control is assessed during the visit.

3.5 Additional Visits

Investigators may schedule additional visits at their own discretion, although no data will be entered on the website. No additional treatment for IXT can be initiated during the study and spectacles (overminus and non-overminus) may not be changed or discontinued during the study.

3.6 Strabismus Surgery or Non-Surgical Treatment

Strabismus surgery and non-surgical treatment of IXT (other than overminus spectacles or non-overminus spectacles) are not allowed during the study.

3.7 Treatment of Amblyopia

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

3.8 Management of Refractive Error

Because of the short duration of the study, the spectacles prescribed at randomization may not be changed or discontinued.

In the event that spectacles are lost or damaged after randomization, the spectacles may only be replaced with the same refraction that was prescribed at randomization.

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS IN FOLLOW-UP

4.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent's contact information. The Jaeb Center will contact the parents of the subjects only when necessary. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the subject and/or family and to help coordinate scheduling of the outcome examinations.

The site investigator or coordinator will directly contact the parents of each subject 2 weeks after randomization to inquire about any issues with obtaining the new spectacles and whether there are any concerns.

4.2 Subject Withdrawals

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

4.3 Risks

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

4.3.1 Risks of Examination Procedures

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

4.3.2 Risk of Overminus Lens Therapy

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

Some subjects treated with overminus lenses may experience eye strain when wearing the spectacles; the eye strain typically dissipates with removal of the spectacles. While some reports in the past have indicated that there may be an increased rate of myopia development when accommodation is stimulated,[25-27] subsequent studies have reported no increase in myopia following overminus lens therapy.[11, 18, 28]

4.3.3 Risk Assessment

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

4.4 Reporting of Adverse Events

Although no adverse events are anticipated as a result of overminus therapy or non-overminus spectacle wear, any new cases of amblyopia or new cases of constant esotropia will be reported. No surgical procedures are part of the protocol and no treatments are being prescribed that are not part of usual care. Investigators will abide by local IRB reporting requirements.

4.5 Discontinuation of Study

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

4.6 Travel Reimbursement

The parent of each subject will be compensated $50 (by check or debit card) for completion of the Enrollment Exam and $50 (by merchandise or money-card) for completion 8-week outcome visit. If there are extenuating circumstances, and the subject is unable to complete the 8-week outcome visit without additional funds due to travel costs, additional funds may be provided.

4.7 Study Costs

The subject or his/her insurance will be responsible for the costs that are considered standard care. Since the Enrollment Exam includes testing procedures that are not standard in all practices and because the 8-week outcome examination is not standard care for all subjects, the cost of these examinations will be paid for by the study.

Study spectacles (overminus spectacles and non-overminus spectacles, including plano spectacles) will be provided by the study after randomization at no cost to the subject. Spectacles reported lost or broken prior to the 8-week outcome visit will be replaced at no cost. The cost to replace spectacles reported lost or broken at or after the 8-week outcome visit will be the responsibility of the subject or his/her insurance company.

Subjects assigned to non-overminus treatment will be offered overminus spectacles at the conclusion of the study, and if the parents elect to pursue such treatment, the cost of the new spectacles will be covered by the study.

The study will not pay for contact lenses.

CHAPTER 5: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

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

The data collected in this short-term, pilot randomized trial will primarily be used to obtain preliminary estimates of treatment effect in both the overminus and non-overminus group to determine whether to proceed to a full-scale, longer-term randomized trial of overminus vs. non-overminus (*section 5.4*).

5.1 Sample Size

As a pilot study, sample size has not been statistically calculated. The sample size of 54 subjects (27 subjects per group) is a convenience sample that is expected to provide at least 50 subjects (25 subjects per group) for analysis after adjusting for up to 5% loss to follow-up.

The primary and secondary analysis sections (*sections 5.2. and 5.3*) indicate the level of statistical power/precision that the sample size of 25 subjects per group (50 total) provides.

5.2 Primary Analysis

The primary analysis will be an intent-to-treat comparison of mean 8-week control of the distance exodeviation (average of 3 measurements) between treatment groups using an analysis of covariance (ANCOVA) model, which adjusts for baseline distance control. Although the primary analysis for the longer-term, full-scale randomized trial will likely be based on a comparison of response rates due to greater interpretability (similar to secondary analysis for the current pilot study described in *section 5.3*), a comparison of means was chosen for the pilot study's primary analysis because it allows for a more powerful statistical comparison of overminus to non-overminus with the small sample size of 25 subjects per treatment group (50 total).

We used the simulated data described in *section 1.12* to determine that the mean difference expected solely from test-retest variability is -0.058 points with a standard deviation of 0.926 points. Given a sample size of 25 subjects per group (50 total), assuming a standard deviation of 0.926, and using a 1-sided t-test with alpha = 0.05, the study will have 88% or greater power to detect a difference between treatment groups if the magnitude of true mean difference in 8-week distance control scores (overminus – non-overminus) is -0.75 points or larger**.** Although a two-sided test could potentially be used in the longer-term, full-scale trial, a one-sided test is being used for the pilot study given that the decision whether to proceed to a full-scale trial is based only on whether overminus is better than the non-overminus control group.

5.3 Secondary Analysis

The secondary analysis will be a treatment group comparison of the proportion of subjects with treatment response, defined as 1 point or more improvement in control of their distance exodeviation between baseline and the 8-week outcome exam. The treatment group comparison of response proportions will use a one-sided Barnard's test with alpha of 0.05, with calculation of a one-sided 95% confidence interval on the difference in proportions with response. In the event that no significant difference between treatment groups is identified, a two-sided 95% confidence interval on the treatment group difference in proportions will also be calculated, the

upper limit of which will estimate the magnitude of effect of overminus that the pilot study failed to detect.

The control group response rate is estimated to be 20% given that the simulations described in *section 1.12* showed that stable subjects (i.e., no real change) would be misclassified as improved 18% of the time using a change of 1 point or more in distance control score (mean of three tests) as the response criteria.

Currently, treatment response is expected to be the primary outcome for the full-scale trial. This pilot study would have 90% or better power to demonstrate a difference between treatment groups of 36% or more (e.g., a 56% in overminus group vs. 20% in non-overminus group). However, the observed data for the response outcome will be evaluated to see whether the mean difference outcome corresponds to a clinically meaningful effect. Observation of a clinically meaningful effect will be considered as supporting a decision to proceed with a full-scale trial, while the opposite will be true if a non-clinically meaningful effect is observed.

Given a sample size of 25 subjects per group (50 total) and assuming response rates of 20% in the non-overminus group, and the overminus response rate at which confidence intervals would be widest (i.e., 54%), the lower limit of a one-sided 95% confidence interval on the difference would be minus 21% and the maximum width of the two-sided 95% confidence interval on the difference would be ±25%.

5.4 Decision Guidelines for Determining Whether to Proceed to a Randomized Trial

The data collected in this short-term, pilot randomized trial will primarily be used to determine whether to proceed to a full-scale, longer-term randomized trial of overminus vs. non-overminus. Two guidelines have been developed to aid in this decision. The first decision guideline evaluates the primary analysis estimate of the treatment group difference in mean distance control scores at 8 weeks. The second decision guideline evaluates the secondary analysis estimate of the treatment group difference in the proportion of subjects with treatment response, defined as an improvement (decrease) of 1 or more points in distance control score at 8 weeks. The results of both decision guidelines are then combined to reach a single conclusion about whether to proceed to a full-scale randomized trial.

In addition to the two decision guidelines, whether to proceed with the full-scale trial will also consider the side effect profiles in each treatment group.

5.4.1 Decision Guideline #1 Based on Treatment Group Difference in Mean Distance Control Score*

The first decision guideline for determining whether to proceed to a full-scale randomized trial evaluates the primary analysis estimate of the treatment group difference in mean distance control scores at 8 weeks. The decision guideline is based on the size of the difference in mean control scores (overminus – non-overminus) and whether it is statistically significant. The decision is:

- **Proceed** if the observed difference favors the overminus group and is statistically significant (diff <0 and p <=0.05)
- **Uncertain** if the observed difference favors the overminus group but is not statistically significant (diff <0 and p >0.05)

- **Do not proceed** if the observed difference is zero or favors the non-overminus group (diff >=0)

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

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

Decision Guideline #1: Whether to Proceed to Full-Scale Randomized Trial Based on OBSERVED Difference in Means in Pilot Study	TRUE Treatment Group Difference (Overminus – Non-overminus) (in points)				
	-0.25	**-0.50**	**-0.75**	**-1.0**	**-1.25**
Proceed** if observed difference is <0 and p <=0.05	24%	59%	88%	98%	>99%
Uncertain if observed difference is <0 and p >0.05	59%	38%	12%	2%	<1%
Do not proceed if observed difference is >=0	17%	3%	0%	0%	0%

* Table cells show the probability of making the given decision if the true difference is the given amount. Estimates were calculated using a 1-sided t-test, a standard deviation of 0.926 and 25 subjects per treatment group.

** The 'proceed' row is the statistical power for detecting a difference using a 1-sided t-test with alpha=0.05 if the true difference is at least the specified magnitude.

As seen in Table 1, there is a high probability of making a 'proceed' decision when the true mean difference is -0.75 point or larger, the probability of an 'uncertain' decision increases as the true mean difference decreases, and the probability of a 'do not proceed' decision is fairly low even for mean differences as small as -0.25 point.

5.4.2 Decision Guideline #2: Based on Treatment Group Difference in Response Rate

The second guideline for determining whether to proceed to a full-scale randomized trial evaluates the secondary analysis estimate of the treatment group difference in the proportion of subjects with treatment response. Because this analysis has lower power than the primary analysis evaluating a difference in mean control scores, the decision guideline for the secondary analysis will be based solely on the point estimate and not statistical significance. The decision is:

- **Proceed** if the overminus group response rate is at least 20% higher than the non-overminus group (difference ≥ 20%)
- **Uncertain** if the overminus group response rate is between 10% to 19% higher than the non-overminus group (difference = 10% to <20%)
- **Do not proceed** if the overminus group response rate is less than 10% higher than the non-overminus group or if the non-overminus group has a higher response rate than the overminus group (difference <10%)

Table 2: Probability of Proceed/Uncertain/Do not Proceed Decisions as a Function of True Response Proportions*

True response proportion in non-overminus group	True response proportion in overminus group	Difference in response (overminus – non-overminus)	Probability of proceed decision (observed difference ≥ 20%)	Probability of uncertain decision (observed difference ≥10% and <20%)	Probability of do not proceed decision (observed difference <10%)
20%	4%	-16%	0%	<0.1%	>99.9%
	8%	-12%	<0.1%	<1%	>99%
	12%	-8%	<1%	3%	96%
	16%	-4%	2%	8%	90%
	20%	0%	6%	13%	81%
	24%	4%	11%	19%	69%
	28%	8%	20%	23%	57%
	32%	12%	32%	25%	44%
	36%	16%	44%	25%	31%
	40%	20%	57%	23%	21%
	44%	24%	68%	18%	14%
	48%	28%	78%	13%	8%
	52%	32%	87%	9%	4%
	56%	36%	91%	6%	3%
	60%	40%	96%	3%	1%
	64%	44%	98%	2%	<1%
	68%	48%	99%	<1%	<1%
	72%	52%	>99%	<1%	<0.1%
	76%	56%	>99%	<1%	<0.1%
	80%	60%	>99%	<1%	<0.1%

*Assuming a sample size of 25 in each group.

Table 2 indicates how likely we are to make certain decisions (proceed, uncertain, do not proceed) if the *true* difference in response between overminus and non-overminus is a specific amount. All rows assume that the true response rate with non-overminus is 20% (based on simulated data, *see section 1.12*).

- For true differences between 0 to -16% (no difference or difference favoring non-overminus, the high probabilities (≥80%) in the 'do not proceed' column indicate that we are very likely to observe a difference <10% if the true difference is 0 to -16%.
- For true differences of 28% or higher favoring overminus, the high probabilities (≥80%) in the 'proceed' column indicate that we are very likely to observe a difference of ≥20% if the true difference is ≥28%.
- For true differences ranging from 4% to 24%, because no one decision has a high probability (≥80%), there is less certainty regarding the decision when the true difference is 4% to 24%.

5.4.3 Combining Decision Guidelines

Table 3 shows how the two decision guidelines will be combined into a single decision on whether to proceed to a full-scale randomized trial.

Table 3: Combining Decision Guidelines to Determine Whether to Proceed to Full-Scale Randomized Trial

Decision Guideline #2 Based on Treatment Group Difference in Response Rate (Overminus – Non-overminus)		**Decision Guideline #1 Based on Treatment Group Difference in Mean Distance Control Score (Overminus – Non-overminus)**		
		diff<0 and p ≤0.05	**diff is <0 and p >0.05**	**diff is ≥0**
	diff ≥ 20%	Proceed	Proceed	Uncertain*
	diff = 10% to <20%	Proceed	Uncertain	Do not proceed*
	diff <10%	Uncertain	Do not proceed	Do not proceed

*Indicates combination which is unlikely to occur—it would require that the >=10% of subjects improved at least 1 point (i.e., response) were offset by many subjects whose control worsened.

5.5 Additional Analyses

All additional analyses will be performed separately for each of the two treatment groups.

5.5.1 Change in Distance Control

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

5.5.2 Change in Near Control

The change in mean near control score from baseline to the 8-week outcome exam and a 95% confidence interval will be calculated for each treatment group.

The proportions and 95% confidence intervals on the proportions of subjects showing improvement, and showing deterioration in their ability to control the near exodeviation at the 8-week outcome visit will be calculated for each treatment group. Improvement will be defined as decrease of 1 point or more in the mean near control score (mean of 3 assessments throughout the examination) between baseline and the 8-week outcome exam.

The distribution of change in near control will also be compared between treatment groups.

5.5.3 Adverse Symptoms

Adverse symptoms will be assessed at enrollment and at the 8-week outcome exam using a simple written symptom survey, which is administered to the parent (*see section 2.4*). Response options are based on frequency of observations; never, almost never, sometimes, often, and always. Scoring of response options is as follows: never = 0, almost never = 1, sometimes =2, often = 3, and always = 4.

The distribution of scores on each symptom survey item will be described for the enrollment exam and the outcome exam for each treatment group. The distribution of change in scores on each symptom survey item will also be described for each treatment group.

5.5.4 Reduction of Distance Visual Acuity

Distance visual acuity will be assessed at enrollment and at the 8-week outcome exam.

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

5.5.5 Reduction of Near Visual Acuity

Binocular near visual acuity will be assessed at enrollment and at the 8-week outcome exam.

The distribution of near visual acuity measures reported as a logMAR value will be described for the enrollment exam and the outcome exam for each treatment group. The distribution of change in visual acuity will also be described for each treatment group.

5.5.6 Compliance of Overminus Wear

Compliance with overminus spectacle wear will be assessed at the 8-week outcome exam. Parents will give an estimate of the proportion of the time their children wore their spectacles. Proportion of time worn will be described as excellent (76% to 100%), good (51% to 75%), fair (26% to 50%), or poor (≤ 25%).

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

5.5.7 Change in Ocular Alignment

Ocular alignment will be measured by PACT at enrollment and the 8-week outcome exam at both distance and near fixation.

The distribution of measures of ocular alignment at distance and near fixation by PACT will be described for the enrollment exam and the outcome exam for each treatment group. The distribution of change in ocular alignment will also be described for each treatment group.

5.5.8 Alternative Approach to Primary Analysis

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

CHAPTER 6: REFERENCES

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