Signature Page

Randomized Trial of Bifocal Spectacles vs. Single Vision Spectacles for Esotropia Greater at Near

Protocol Identifying Number: ETS3

Version Number: 1.1

June 1, 2022

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KEY ROLES

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List of Abbreviations

ABBREVIATION	DEFINITION
Δ	Prism diopters
AC/A	Accommodative convergence to accommodation ratio
ANCOVA	Analysis of covariance
arcsec	Seconds of arc
ATS	Amblyopia Treatment Study
ATS-HOTV	Amblyopia Treatment Study HOTV visual acuity testing protocol
ETS	Esotropia Treatment Study
CC	Coordinating Center
CI	Confidence interval
BFL	Bifocal Lenses
CFR	Code of Federal Regulations
CR	Cycloplegic refraction
CRF	Case report form
D	Diopter
DSMC	Data safety and monitoring committee
DVD	Dissociated vertical deviation
eCRF	Electronic case report form
E-ETDRS	Electronic Early Treatment of Diabetic Retinopathy Study visual acuity protocol
ET	Esotropia
EVA	Electronic visual acuity tester
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IOD	Interocular difference
IRB	Institutional Review Board
IXT	Intermittent exotropia
JCHR	Jaeb Center for Health Research
log arcsec	Logarithm of seconds of arc
logMAR	Logarithm of the minimal angle of resolution
ME	Masked examiner
NIH	National Institutes of Health
PACT	Prism and alternate cover test
PEDIG	Pediatric Eye Disease Investigator Group
RPS	Randot Preschool Stereoacuity test
SE	Spherical equivalent refractive error (Sphere + ½ Cylinder)
SPCT	Simultaneous prism and cover test
SVL	Single-vision lenses
TF	Trial frames
VA	Visual acuity
VT	Vision therapy

PRINCIPAL INVESTIGATOR AGREEMENT FOR PROTOCOL
Randomized Trial of Bifocal Spectacles vs. Single Vision Spectacles for Esotropia Greater at Near (ETS03)

Each clinical site that is approved to participate in the ETS03 study will have one individual designated as the Protocol Principal Investigator (Protocol PI) at the site for this protocol. This investigator may or may not be the same investigator that serves as the overall Network Site Principal Investigator (Site PI) for all PEDIG studies.

The Protocol PI and the Site PI (if different) agree to the following for the ETS03 study – They will:

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

Given the amount of time and effort required for site personnel to become certified for the study (and for the Coordinating Center to manage the site), the PEDIG Executive Committee is asking each interested site to declare the number of participants meeting ETS03 protocol criteria they feel they can enroll into the study.

After review of ETS03 eligibility criteria with participating site staff, and retrospective chart review, Site ___ ___ ___ commits to enroll 3 new participants each year for 4 years and to follow them for the duration of the study.

If you feel you do not see a sufficient number of eligible patients who are likely to enroll into the study each year, we ask that you not pursue certification for the study.

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

- Understand the importance of successful follow-up and retention of those enrolled at our site.
- Agree that the site has the potential and commits to enroll the number of participants stated above per year once certified.

Protocol Principal Investigator's Signature _____Date: _____ / _____ / _____

Name: _____

To be completed only if different:
Network Site Principal Investigator's Signature _____Date: ____ / ____ / ____

Name: _____ Site #: _____

Protocol Summary

	DESCRIPTION
Title	Randomized Trial of Bifocal Spectacles vs. Single Vision Spectacles for Esotropia Greater at Near
Précis	The study is being conducted to compare whether an optical correction of bifocal spectacle lenses (BFL) or single-vision spectacle lenses (SVL) is more effective for the treatment of children with esotropia greater at near. Children will be randomized to be treated with BFLs or SVLs for 3 years and be evaluated at regular intervals throughout the study to determine whether their condition has worsened. Children whose condition worsens during the study will either start BFL treatment (if randomized to SVL group) or continue BFL treatment (if randomized to BFL group) for 2 months to allow assessment of outcome in BFLs, and then be released to treatment at investigator discretion while continuing in study follow-up. Children whose condition has not worsened during the study will start or continue BFL (depending on treatment group) for 2 months at 3 years. All children return at 38 months to assess binocular function. The effectiveness and safety of both treatments will be compared.
Objectives	• To compare the proportion of BFL and SVL participants with treatment failure by 36 months • To compare binocular function test scores between the BFL and SVL groups with both groups in BFL at 38 months after randomization (or 2 months after treatment failure) • To evaluate treatment failure by 36 months according to baseline factor subgroups of: duration of constant esotropia pre-enrollment, presence of near stereoacuity on the Randot Preschool Stereoacuity test, in-office response of near alignment with +3.00 D lenses, and gradient AC/A ratio
Study Design	Multicenter, randomized clinical trial
Number of Sites	Up to 70 PEDIG sites will participate in the study.
Endpoint	**Primary Effectiveness Outcome:** *Treatment failure* defined as meeting any one of the following criteria at any follow-up visit between 3 months to 36 months inclusive: 1. Distance motor failure: Constant ET ≥15Δ by SPCT at distance. (NOTE: intermittent esotropia and esophoria of any magnitude are NOT considered failures). 2. Near stereo failure: Decrease in near stereoacuity on the Randot Preschool Stereotest of 2 or more levels from baseline or from 960" at baseline to nil (*criteria not applicable if nil near stereo at baseline)* • Baseline stereoacuity is defined as the near stereoacuity performed with +3.00 D added to the participant's enrollment distance spectacle correction in trial frames. • At all follow-up visits, the best of two stereo measures in the OFFICE lenses will be used to determine treatment failure. • Stereoacuity values are calculated for the 33 cm test distance required for testing through the added +3.00 D lenses at near (instead of the standard 40 cm). • **NOTE:** Participants without measurable near stereoacuity at baseline cannot fail by stereoacuity criteria. 3. Binocular diplopia with a frequency of "more than 2 times per day" over the last week by parental report 4. Nonsurgical or surgical treatment for ET, other than the randomized treatment, is started before a failure criterion is met **Key Secondary Effectiveness Outcomes:** Binocular function test score with both groups in BFLs 2 months following failure or at the 38-month visit, if no failure (whichever comes first). **Key Safety Outcomes:** Distance motor or near stereo failure, reduction of distance visual acuity of ≥0.2 logMAR

	DESCRIPTION

Population	**Inclusion Criteria for Enrollment:**
	• Age 3 to <9 years
	• Esodeviation meeting all the following criteria is present in refractive correction (if required or worn)
	  o Constant or intermittent esotropia ≥10Δ measurable by SPCT at near
	  o Distance esotropia (constant, intermittent), esophoria, or orthophoria, with near esodeviation ≥10Δ larger than distance deviation by PACT
	  ▪ If constant ET at distance, then must be ≤6Δ by SPCT
	  ▪ If intermittent ET or esophoric at distance, can be any magnitude at distance (as long as near esodeviation is ≥10Δ larger than distance deviation by PACT)
	• Cycloplegic refraction within past 3 months (but not on day of exam)
	• Wearing spectacles for at least 4 weeks if refractive error is 0.75 D SE or more
	• Spectacles (if worn) must meet the following criteria:
	  o SE refractive error must be corrected within ±0.625 D
	  o Sphere power must be corrected within ±0.50 D
	  o Anisometropia must be corrected within ±0.50 D SE
	  o Cylinder power must be corrected within ±0.50 D
	  o Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D.
	• Best-corrected VA meeting the following criteria:
	  o Better-seeing eye VA is age-normal (see section 2.2)
	  o IOD in VA within 0.2 logMAR (although previous amblyopia is allowed)
	  o Worse-seeing eye VA of 20/63 or better
	• Investigator and parent willing to forgo treatment of ET other than assigned randomized treatment for 36 months unless failure criteria are met.
	• Investigator willing to prescribe BFL-spectacles only (in both treatment groups) for 2 months after meeting failure criteria (if failed prior to 36 months); otherwise, between 36 and 38 months
	
	Exclusion Criteria for Enrollment:
	• Previous BFL wear (SVL spectacle wear of any duration is allowed)
	• Current or planned contact lens wear over the next 3 years
	• Myopic refractive error of more than -6.00 D SE
	• Previous strabismus surgery (including Botox injection), intraocular surgery (e.g., laser, anti-VEGF injection, or cataract), extraocular surgery (e.g., scleral buckle), or refractive surgery
	• Previous treatment for ET using miotics, VT, or prism within prior 3 months
	• Amblyopia treatment other than refractive correction within prior 3 months
	• Vertical deviation ≥3Δ at distance or near by PACT
	• Oculomotor findings consistent with infantile ET (e.g., latent nystagmus, manifest nystagmus, DVD)
	• AV pattern: ≥10Δ difference between upgaze and downgaze by PACT at distance
	• Paretic or restrictive strabismus
	• Constant exotropia at near when tested through the +3.00 D add (intermittent XT and exophoria are allowed)
	• Diplopia “more than 2 times per day” over the last week prior to enrollment by parental report. The frequency of diplopia, if any, must be “2 times or less per day” to be eligible.
	• Significant developmental delay that would interfere with child’s ability to complete testing
	• Neurological conditions that could affect ocular motility (e.g., cerebral palsy, Down syndrome)
	• Immediate family member (child or sibling) of any site personnel directly affiliated with the study

Sample Size	444 participants randomized (approximately 222 per treatment group)
Phase	Phase 3
Treatment Groups	Random assignment (1:1) to:

	DESCRIPTION
	• Single vision spectacles (SVLs) • Bifocal spectacles (BFLs): +3.00 D flat-top 35
Duration of Participation	38-40 months after randomization
Protocol Overview/Synopsis	Participants will be randomly assigned to treatment with a BFL or SVL spectacle correction for 3 years. Generally, participants will be followed at 3-month intervals for the first year and every 6 months thereafter until the primary outcome visit at 36 months. At each follow-up visit between 3 months and 36 months, ocular alignment and stereoacuity will be assessed to determine if any of the three study-specified failure criteria have been met (worsening of distance ET, reduction in near stereoacuity, or frequent diplopia ("more than 2 times per day" over the last week). The primary outcome is failure at or before 36 months. If a failure criterion is met between 3 to 30 months, participants randomized to SVLs will be prescribed BFLs and those in BFLs will be prescribed continued BFLs. Participants in both groups will return in BFLs 2 months after failure for a Post-failure Secondary Outcome Visit to determine the child's binocular function, after which the child will be released to treatment at investigator discretion. Participants with confirmed failure who complete the Post-failure Secondary Outcome Exam will return for the 12- and 24-month follow-up visits (abbreviated testing) as well as the 38-month Secondary Outcome Visit (they will not return for the 36-month Primary Outcome visit). If a failure criterion is <u>not</u> met between 3 to 30 months, participants without confirmed failure will complete the 36-month Primary Outcome Visit, After the 36-month visit, SVL group participants will be prescribed BFLs and BFL participants will continue using BFLs. All participants (i.e., regardless of failure status) will return for a 38-month Secondary Outcome Visit to assess binocular function.

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Study Summary Flow Chart

Eligibility Criteria for Enrollment

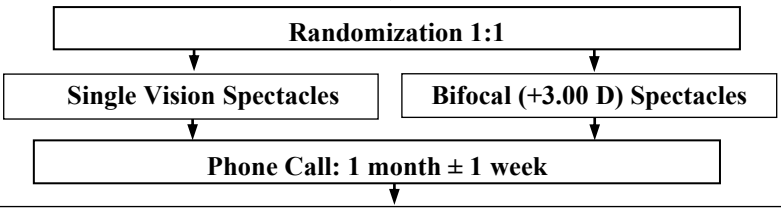
- Age 3 to < 9 years
- Esodeviation meeting all the following criteria in refractive correction (if required or worn)
  - Constant or intermittent esotropia ≥10Δ measurable by SPCT at near
  - Distance esotropia (constant, intermittent), esophoria, or orthophoria, with near esodeviation ≥10Δ larger than distance deviation by PACT
    - If constant ET at distance, then must be ≤6Δ by SPCT
    - If intermittent ET or esophoric at distance, can be any magnitude at distance (as long as near esodeviation is ≥10Δ larger than distance deviation by PACT)
- Better-seeing eye VA is age normal
  - 3 years: 20/50 or better
  - 4 years: 20/40 or better
  - 5-6 years: 20/32 or better
  - 7-12 years: 20/25 or better
- IOD in VA within 0.2 logMAR
- Worse-seeing eye VA is 20/63 or better
- Cycloplegic refraction within 3 months (but not on day of exam)
- Wearing spectacles if refractive error is 0.75 D SE or more
- Current spectacles (if worn) meeting all the following:
  - Worn for at least 4 weeks
  - SE refractive error must be corrected within ±0.625 D
  - Sphere power must be corrected within ±0.50 D
  - Anisometropia must be corrected within ±0.50 D SE
  - Cylinder power must be corrected within ±0.50 D
  - Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D.

Exclusion Criteria for Enrollment

- Previous BFL wear (SVL wear of any duration is allowed)
- Current or planned contact lens wear over the next 3 years
- Myopia more than -6.00 D SE
- Previous strabismus surgery (including Botox), intraocular surgery, extraocular surgery, or refractive surgery
- Previous treatment for ET using miotics, VT or prism within prior 3 months
- Amblyopia treatment other than refractive correction within prior 3 months
- Vertical deviation ≥3Δ at distance or near by PACT
- Oculomotor findings consistent with infantile ET (e.g., latent nystagmus, manifest nystagmus, DVD)
- AV pattern ≥10Δ difference between upgaze and downgaze by PACT at distance
- Constant exotropia at near during enrollment visit when tested through +3.00 D add (intermittent XT and exophoria are allowed)
- Paretic or restrictive strabismus
- Diplopia "more than 2 times per day" over the last week prior to enrollment by parental report
- Significant developmental delay that would interfere with child's ability to complete testing
- Neurological condition that could affect ocular motility (e.g., cerebral palsy, Down syndrome)
- Immediate family member (child or sibling) of any investigative site personnel directly affiliated with the study

Enrollment Exam Test Procedures

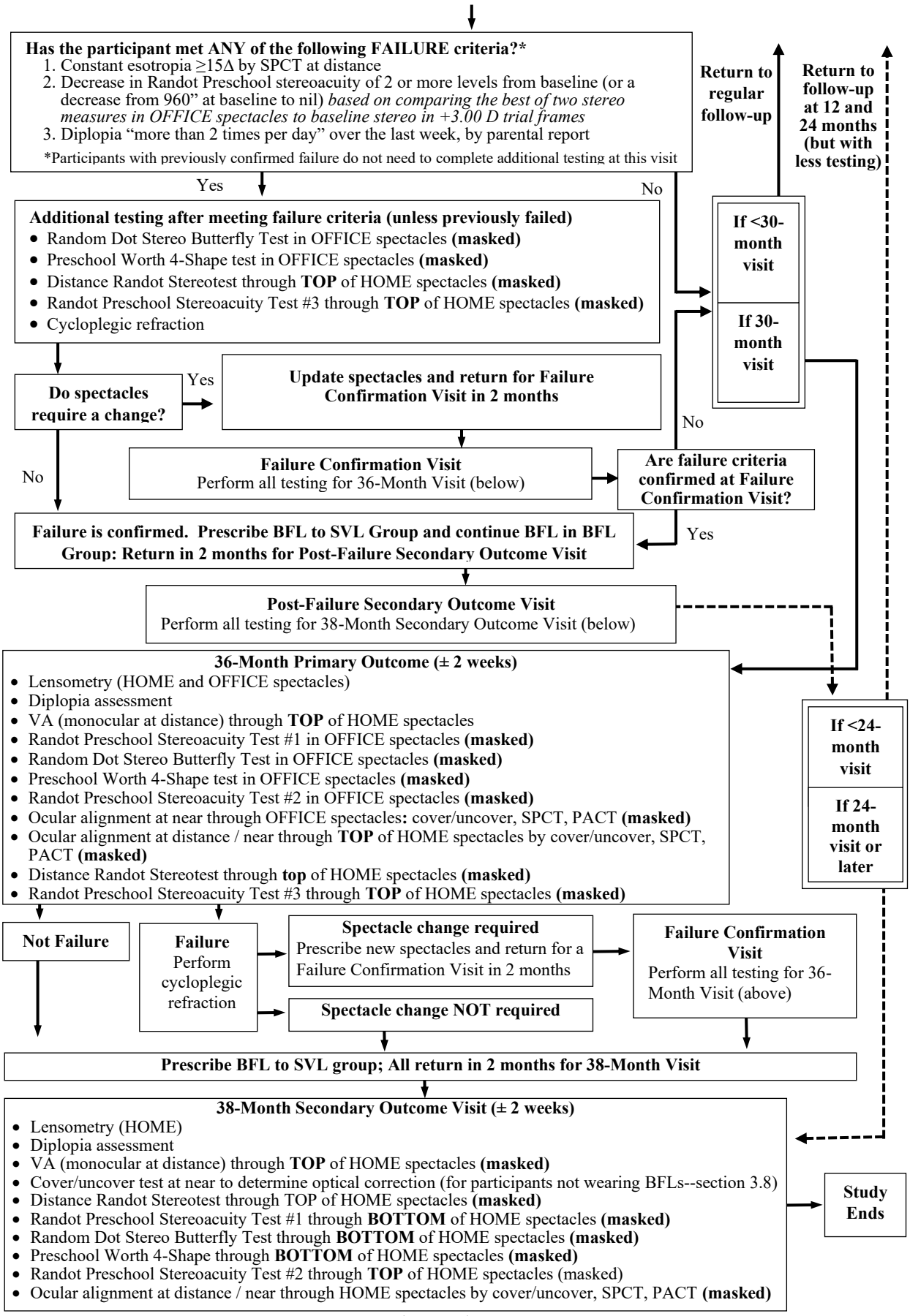
- Lensometry
- Diplopia assessment
- VA in spectacle correction (if worn): measured by ATS-HOTV; e-ETDRS; OR crowded single-optotype or single-line HOTV, LEA SYMBOLS, or Snellen letters
- Randot Preschool Stereoacuity Test in spectacles (if worn)
- Distance Randot Stereotest in spectacles (if worn)
- Randot Preschool Stereoacuity Test in TF with +3.00 added lenses
- Random Dot Stereo Butterfly Test in TF with +3.00 added lenses
- Preschool Worth 4-Shape test in TF with +3.00 added lenses
- Near ocular alignment in TF with +3.00 added lenses
- Distance and near ocular alignment in spectacles (if worn)



3-, 6-, 9-, 12-, 18-, 24-, and 30-Month Visits (± 2 weeks)

- Lensometry (HOME and OFFICE spectacles)
- Diplopia assessment
- VA (monocular at distance) through top of HOME spectacles*
- Randot Preschool Stereoacuity Test #1 in OFFICE spectacles **(masked**)
- Ocular alignment at near in OFFICE spectacles: cover/uncover, SPCT, PACT **(masked)**
- Ocular alignment at distance / near through top of HOME spectacles: cover/uncover, SPCT, PACT **(masked)**
- Randot Preschool Stereoacuity Test #2 in OFFICE spectacles (**masked)**
- Cycloplegic refraction (12-, 24-, and 30-month visits only) – *and performed after additional testing if failure criteria met at any visit*

*** HOME spectacles are the spectacles prescribed at randomization that are worn full-time when not in the office. OFFICE spectacles are the SVL spectacles with +3.00 D over CR – kept in the office and used for masked testing only.**


Has the participant met ANY of the following FAILURE criteria?*
1. Constant esotropia ≥15Δ by SPCT at distance
2. Decrease in Randot Preschool stereoacuity of 2 or more levels from baseline (or a decrease from 960" at baseline to nil) based on comparing the best of two stereo measures in OFFICE spectacles to baseline stereo in +3.00 D trial frames
3. Diplopia "more than 2 times per day" over the last week, by parental report
*Participants with previously confirmed failure do not need to complete additional testing at this visit
Yes
No
Return to regular follow-up
Return to follow-up at 12 and 24 months (but with less testing)
Additional testing after meeting failure criteria (unless previously failed)
Random Dot Stereo Butterfly Test in OFFICE spectacles (masked)
Preschool Worth 4-Shape test in OFFICE spectacles (masked)
Distance Randot Stereotest through TOP of HOME spectacles (masked)
Randot Preschool Stereoacuity Test #3 through TOP of HOME spectacles (masked)
Cycloplegic refraction
If <30-month visit
If 30-month visit
Do spectacles require a change?
Yes
Update spectacles and return for Failure Confirmation Visit in 2 months
No
No
Failure Confirmation Visit
Perform all testing for 36-Month Visit (below)
Are failure criteria confirmed at Failure Confirmation Visit?
Yes
Failure is confirmed. Prescribe BFL to SVL Group and continue BFL in BFL Group: Return in 2 months for Post-Failure Secondary Outcome Visit
Post-Failure Secondary Outcome Visit
Perform all testing for 38-Month Secondary Outcome Visit (below)
36-Month Primary Outcome (± 2 weeks)
Lensometry (HOME and OFFICE spectacles)
Diplopia assessment
VA (monocular at distance) through TOP of HOME spectacles
Randot Preschool Stereoacuity Test #1 in OFFICE spectacles (masked)
Random Dot Stereo Butterfly Test in OFFICE spectacles (masked)
Preschool Worth 4-Shape test in OFFICE spectacles (masked)
Randot Preschool Stereoacuity Test #2 in OFFICE spectacles (masked)
Ocular alignment at near through OFFICE spectacles: cover/uncover, SPCT, PACT (masked)
Ocular alignment at distance / near through TOP of HOME spectacles by cover/uncover, SPCT, PACT (masked)
Distance Randot Stereotest through top of HOME spectacles (masked)
Randot Preschool Stereoacuity Test #3 through TOP of HOME spectacles (masked)
If <24-month visit
If 24-month visit or later
Not Failure
Failure
Perform cycloplegic refraction
Spectacle change required
Prescribe new spectacles and return for a Failure Confirmation Visit in 2 months
Spectacle change NOT required
Failure Confirmation Visit
Perform all testing for 36-Month Visit (above)
Prescribe BFL to SVL group; All return in 2 months for 38-Month Visit
38-Month Secondary Outcome Visit (± 2 weeks)
Lensometry (HOME)
Diplopia assessment
VA (monocular at distance) through TOP of HOME spectacles (masked)
Cover/uncover test at near to determine optical correction (for participants not wearing BFLs--section 3.8)
Distance Randot Stereotest through TOP of HOME spectacles (masked)
Randot Preschool Stereoacuity Test #1 through BOTTOM of HOME spectacles (masked)
Random Dot Stereo Butterfly Test through BOTTOM of HOME spectacles (masked)
Preschool Worth 4-Shape through BOTTOM of HOME spectacles (masked)
Randot Preschool Stereoacuity Test #2 through TOP of HOME spectacles (masked)
Ocular alignment at distance / near through HOME spectacles by cover/uncover, SPCT, PACT (masked)
Study Ends

Schedule of Study Visits and Procedures

	Enrollment / Randomization Visit	3 to 30-month Visits (3, 6, 9, 12, 18, 24, and 30)[c]	36-Month Visit (Primary Outcome)[f]	Failure Confirmation Visit	Post-failure Secondary Outcome Visit[h]	38-Month Secondary Outcome Visit[g]
Consent/Assent	X	----	----	----	----	----
Demographic Information / Ocular History	X	X	X	X	X	X
Lensometry	X	Home and Office	Home and Office	Home and Office	Home	Home
Diplopia Assessment	X	X	X	X	X	X
Visual Acuity (monocular distance)[a]	X	Home[top]	Home[top]	Home[top]	Home [top]	Home [top]
Cover-uncover Test at Near (if not wearing BFLs at 38 months)[g]						ME Home[bot]
Randot Preschool Stereoacuity Test (33 cm) #1	X	ME Office	ME Office	ME Office	ME Home [bot]	ME Home [bot i]
Distance Randot Stereotest (3 m)	X	if fails[d] ME Home[top]	ME Home[top]	ME Home[top]	ME Home [top]	ME Home [top]
Randot Preschool Stereoacuity Test (33 cm) #2	TF+3	ME Office	ME Office	ME Office	ME Home[top]	ME Home[top]
Random Dot Stereo Butterfly Test (33 cm)	TF+3	if fails[d] ME Office	ME Office	ME Office	ME Home [bot]	ME Home [bot g]
Preschool Worth 4-Shape (at 33 cm)	TF+3	if fails[d] ME Office	ME Office	ME Office	ME Home [bot]	ME Home [bot g]
Ocular Alignment at distance and near (in study spectacles as specified)	X	ME Home[top]	ME Home[top]	ME Home[top]	ME Home	ME Home
Ocular Alignment at near through +3.00 D	TF+3	ME Office	ME Office	ME Office	----	----
Randot Preschool Stereoacuity Test (33 cm) #3	----	If fails[d] ME Home[top]	ME Home[top]	ME Home[top]	----	----
Cycloplegic Refraction	----	12, 24, 30-mos, and if fail	If fail		----	----
Prescribe Spectacles	X[b]		X[e]	X[g]		

TF + 3.00 = trial frames with current refractive correction worn at enrollment (or plano, if emmetropia) with +3.00 D. The two sphere powers should be added and a single lens used for the spherical power component of the trial frames.

BFL^{top} = participant viewing through top portion of bifocal lenses (looking over BFL segment)

BFL^{bot} = participant viewing through the BFL segment situated at the bottom of the lenses

Home = randomized spectacles worn full-time when not in the office

$Home^{top}$ = randomized spectacles worn full-time when not in the office with participant viewing through top (distance) portion with bottom half taped (for masking)

ME = masked examiner

Office = SVLs comprised of cycloplegic refraction with +3.00 D added (to be kept at clinic for testing)

[a] Visual acuity can be completed at the end of the visit, if desired.

[b] Prescribe assigned spectacles per randomization (BFLs or SVLs)

[c] Participants with confirmed failure prior to the 36-month Primary Outcome visit and completing their Post-failure Secondary Outcome Visit will only return for interim follow-up visits at 12 and 24 months with abbreviated testing (monocular distance VA, near stereoacuity, and ocular alignment).

[d] Additional testing is completed if a failure criterion is met prior to the 36-month visit (and failure has not been met and confirmed at a prior visit). Additional testing must be done prior to the cycloplegic refraction.

[e] At the 36-month visit, prescribe BFLs for participants randomized to the SVL group; continue BFLs for those randomized to the BFL group. The exceptions are: 1) participants who met confirmed failure criteria at a previous visit, who underwent 2 months of BFL spectacle wear and the Post-Failure Secondary Outcome Visit, and who now continue with treatment (or no treatment) at investigator discretion; and 2) participants who have unconfirmed failure at 36 months, who have their randomized treatment spectacles updated and return to have failure confirmed/not confirmed at the Failure Confirmation Visit.

[f] 36-month Primary Outcome Visit not required for participants with previously confirmed failure.

[g] For visits prior to 36 months:

- If failure NOT CONFIRMED, continue current randomized spectacle correction
- If failure CONFIRMED, prescribe BFL spectacles for participants in the SVL group; continue BFL spectacles for the BFL group.

For the 36-month Visit, prescribe BFL spectacles for participants in the SVL group; continue BFL spectacles for the BFL spectacles group regardless of whether failure is confirmed.

[h] At the Post-Failure Secondary Outcome Visit, all participants are expected to be wearing HOME spectacles that are BFL.

[i] All participants will have a 38-month Secondary Outcome Visit, even if they have had a previous Post-failure Secondary Outcome Visit. Regarding the timing of the visit, note that participants who meet failure criteria at 36 months (and have not failed previously) and need their spectacles updated will have a Failure Confirmation Visit 2 months later (4-12 weeks) and return at 40 months for their 38-month Secondary Outcome Visit. Most participants are expected to be wearing HOME spectacles that are BFLs, in which case participants should look through the top portion (distance correction) of their HOME spectacles for all tests requiring distance viewing and look through the bottom of their HOME spectacles for all near testing done at 33 cm. For participants who are not wearing BFLs, a cover/uncover test at near should be performed to determine the optical correction to be used for testing. If the participant has an esotropia at near on cover/uncover testing, then most near testing (section 3.8) must be completed through added +3.00 lenses at near. This can be done by 1) placing +3.00 lenses in Halberg/Janelli clips over their current HOME SVL lenses or 2) using a trial frame with a lens power that is +3.00D more than their HOME spectacle correction; if no esotropia is present, near testing must be completed through the HOME spectacles.

Chapter 1: Background Information

1.1 Introduction

Childhood-onset esotropia (ET) affects between 0.9% and 2.3% of children in the United States.[1-4] In some types of ET, the near angle of deviation exceeds the distance deviation. This type of esodeviation was first described by Duane in 1897[5] and has subsequently been referred to as either near-distance disparity ET,[6] non-refractive accommodative ET,[7] high accommodative convergence/accommodation (AC/A) ratio ET,[8, 9] or convergence excess ET.[10-13] Different approaches have been employed when classifying and sub-classifying this type of esodeviation, resulting in considerable inconsistency across studies, with added confusion arising from the same terminology being used to describe different clinical entities. Notwithstanding differing opinions regarding classification and terminology, there is common recognition of a distinct type of esodeviation, characterized by manifest ET at near fixation, but with less esodeviation (including orthophoria or intermittent ET) at distance fixation.[6-8, 10-14] For the purpose of this study, we refer to this type of esodeviation as "ET greater at near."

By most definitions, ET greater at near is characterized by orthotropia or microesotropia at distance fixation, often with some evidence of motor fusion and stereoacuity,[11] with the ET at near measuring at least 10 prism diopters (Δ) greater than the esodeviation at distance fixation.[6-8, 10-14] When the esodeviation is manifest at near, suppression typically occurs, or (more rarely) the patient may experience diplopia.[12] While different sub-types of ET greater at near have been described, differentiated primarily by the presence or absence of a high AC/A ratio,[7, 10, 11, 15] few previous studies have evaluated the effects of treatment in these potential diagnostic sub-groups. The average age at onset of ET greater at near is reported to be between 2 and 3 years of age.[11, 16]

1.2 Current Practice

Initial treatment for ET greater at near usually includes full (or nearly full) correction of hyperopic refractive error measured by cycloplegic refraction. There is debate, however, over whether additional treatment should be implemented, and if so, what form that treatment should take.[10, 17] Some practitioners monitor the patient in single vision lenses (SVLs) (where needed for correction of refractive error), whereas others prescribe additional treatment out of concern that persistent near ET may cause decompensation of the distance ET, loss of stereoacuity and binocularity, and/or symptoms including diplopia. Possible treatment options are bifocal lenses (BFLs), strabismus surgery, or miotic eye drops, with BFLs being the most commonly prescribed treatment in the US.[10, 11]

1.3 Potential Benefits of Treatment with Bifocal Lenses and Single Vision Lenses

1.3.1 Treatment with Bifocal Lenses (BFLs)

Bifocal spectacle lenses have added plus power in the lower portion of the lenses that is designed to be used for near viewing. These lenses reduce the amount of accommodation exerted at near, with the aim of reducing the associated convergence response. The strength of the BFLs prescribed for young children with ET greater at near is often +3.00 D or the minimum amount of plus power required to achieve near motor alignment or improved stereoacuity at near.[18, 19] For some eyecare providers, the aim of BFL treatment is to eventually achieve motor alignment at near without the BFLs, and thus they attempt to gradually reduce the strength of the BFL until motor alignment can be maintained without the BFLs. Others use a BFL prescription to facilitate

alignment of the eyes at near with improved stereopsis to delay or avoid strabismus surgery, sometimes keeping the child in BFLs for years provided the BFLs continue to facilitate straight-eye alignment and normal sensory fusion. The reported duration of BFL treatment varies considerably and can continue for many years.[20]

1.3.2 Treatment with Single Vision Lenses (SVLs)

Those who prescribe SVLs for ET greater at near (if needed for the correction of refractive error) believe there is no functional advantage to BFLs when the child's eyes are aligned (or nearly aligned if a small-angle ET is present) at distance and the child does not experience diplopia or other bothersome symptoms at near. Subjectively, such a child is asymptomatic, and may have binocular alignment for considerable portions of the day (i.e., when not viewing at near), and in such cases, providing reassurance that the capacity for binocular single vision is being retained. Indeed, some proponents of SVLs have hypothesized that SVLs allow fusional divergence amplitudes to increase over time, thereby enabling better control of the esodeviation, whereas development of fusional divergence amplitudes with BFLs may be limited.[8] SVLs also have the advantage of lower cost, and (at least anecdotally) may be preferred by some children over BFLs for psychosocial reasons.

1.4 Studies Evaluating BFLs and SVLs

1.4.1 Comparative Studies of BFLs versus SVLs

There are few previous studies comparing BFL and SVL treatments for ET greater at near.[8, 13] Of those available, outcomes are sometimes reported "on-treatment" (i.e., still wearing BFLs) and sometimes after discontinuation of treatment (often considering the inability to successfully wean the child off of BFLs as a failure of BFLs). The following review of previous studies focuses primarily on outcomes while on treatment.

We are aware of two previous studies reporting on-treatment outcomes for both BFLs and SVLs for ET greater at near. In the first study, Pratt-Johnson & Tillson[13] performed a retrospective review of children with ET greater at near whose parents had been offered the choice of BFL treatment or SVL treatment. In all cases, the treatment of choice started before 4 years of age and the outcome was assessed after 6 years of age (majority older than 8 years of age), with an average of 4 years of follow-up (range 4 to 16 years). Eighty patients were identified with less than 10Δ of ET at distance and with an ET of 30Δ or greater at near. Of these 80, 40 chose SVLs and 40 chose treatment with BFLs. Sensory outcomes, while wearing the chosen lenses, were classified as either: central fusion (positive fusion using central fusion slides on the synoptophore and having 60 arcsec or better on the Titmus stereotest), peripheral fusion (using peripheral fusion slides on synoptophore and having at least 8Δ of peripheral motor fusion), or no fusion. At final follow-up, there were no differences in the proportions of participants with each of the three sensory outcomes: central fusion: 3/40 (7.5%) with BFLs vs 2/40 (5%) with SVLs; peripheral fusion: 32/40 (80%) vs 34/40 (85%) respectively; no fusion: 5/40 (12.5%) vs 4/40 (10%), respectively. There was also no difference in the proportion of participants decompensating (increasing in distance eso magnitude) and going on to surgery: 9/40 (22.5%) in the BFL group and 5/40 (12.5%) in the SVL group. Similar findings were reported in a smaller study by the same authors, published the previous year.[17]

In the second, more recent study, Whitman et al[8] retrospectively reviewed the charts of 180 children with ET greater at near, with the aim of comparing on-treatment stereopsis outcomes in

those prescribed BFLs (mean age 5.1±2.1 years) versus SVLs (mean age 5.4±2.2 years). All patients had less than a 10Δ ET at distance (by PACT), more than 10Δ ET at near, with the near ET measuring at least 10Δ greater than the distance. At baseline, all patients also had either fusion on the Worth 4-dot, stereopsis, or improvement in the near angle to less than 10Δ when tested through +3.00 D lenses. Treatment was at practitioner discretion: 77/180 were treated with BFLs and 103/180 were treated with SVLs. Of note, patients treated with BFLs had a larger magnitude of ET at near at baseline, but stereopsis at baseline was similar between groups. After approximately 4 years of follow-up, stereoacuity was found to be similar between those wearing BFLs and those wearing SVLs (5.94±2.3 log arcsec [379 arcsec] in the BFL group vs 5.59±2.1 log arcsec [268 arcsec] in SVL group). An additional primary outcome reported by the authors was the risk of surgery, which in all cases was performed due to an increase in the distance angle of deviation to greater than 10Δ (average increase from baseline was 25Δ in the BFL group and 20.5Δ in the SVL group). More patients prescribed BFLs went on to have surgery (12 of 77; 15.6%; 95% CI = 9.2% to 25.3%) compared with those wearing SVLs (4 of 103; 3.9%; 95% CI = 1.5% to 9.6%) (difference: 11.7%, 95% CI = 3.1% to 21.7%), but it is important to note that the BFL group had a larger angle of deviation at baseline. In addition, the authors acknowledged that some investigators may have put patients in BFLs as a "last ditch" attempt at treatment before going to surgery, which could ostensibly be responsible for the higher risk of surgery in the BFL group.[8]

1.4.2 Bifocal Lenses – On-Treatment Outcomes

Other studies have reported on-treatment outcomes for BFLs with regard to treatment failure. Arnoldi[11] reported on 22 patients with ET greater at near treated with BFLs (age not reported) who were initially aligned through the BFL segment; 7 (35%) later developed an ET through the BFLs and 2 (10%) developed an ET at distance and underwent surgery. Von Noorden et al[21] retrospectively reviewed 84 patients with convergence excess ET (some of whom had undergone previous surgery), who were treated with BFLs with the aim of weaning the BFL power over time. They reported that 14/84 (17%) who showed initial control of the near ET through the BFLs subsequently lost fusional control at near through the BFLs despite having been prescribed a bifocal add up to +3.50 D.

1.4.3 Single Vision Lenses – On-Treatment Outcomes

Gerling and Arnoldi[19] retrospectively evaluated the effectiveness of SVLs in 23 children (mean 2.9, range 0.5 to 8 years) with ET greater at near, all of whom had a high AC/A ratio (>5.6:1). After 5 years of follow-up they classified the near magnitude of deviation, control of the deviation (categorized as either: phoria, intermittent, or tropia), change in refractive error, and stereopsis as either: 1) stable (near angle measurements within 5Δ of baseline, no change in control [implied at distance or near], no change in refraction [within 0.50 D of baseline refraction], and no change in near stereopsis category [fine stereo: better or equal to 60 arcsec; gross stereopsis 70 arcsec or worse; no stereopsis]), 2) improved (near angle decreased more than 5Δ, control improved [implied at distance or near], refraction decreased more than 0.50 D, and near stereopsis improved), or 3) deteriorated (increase in near angle of more than 5Δ, deterioration in control [implied at distance or near], an increase in refraction of more than 0.50 D, and a loss of near stereopsis). The near angle of deviation improved in 15/23 (65%), was stable in 8/23 (35%), and deteriorated in none (distance angle not reported). Control, categorized as improvement, stable, or deterioration over follow-up improved in 13/23 (56%) and was stable in 10/23 (44%). Stereopsis category improved at some point during follow-up in 8 of the 18

(44%) for whom there were repeated stereopsis measurements, and stereopsis remained stable in 10/18 (56%).

1.4.4 Potential Risks of BFL Spectacles

The possibility of harm from BFL wear has been raised in some previous studies. Fresina et al[7] prospectively evaluated potential harm (defined as a deficiency in accommodation) from BFLs in 28 children with ET greater at near, all of whom were prescribed BFLs. Near point of accommodation was measured at baseline (before the BFL prescription was prescribed) and measured again after 4 years of wearing BFLs. Near point of accommodation was found to be below normal in 10/28 at baseline with no significant changes at the 4-year outcome, leading the authors to conclude that while some patients with ET greater at near have a baseline accommodation deficit, BFL wear does not reduce the ability to accommodate.

The other potential harm from BFL wear is a higher likelihood of surgery. Although Pratt-Johnson and Tillman[13] found there was no higher likelihood of surgery, Whitman et al[8] concluded that there was a higher likelihood of surgery in their patients treated with BFLs. Nevertheless, the Whitman et al[8] conclusions are confounded by the presence of a larger angle of deviation in those being prescribed BFLs. In addition, there is a possibility of practitioner bias, with those more likely to prescribe BFLs also being those more likely to perform surgery. It remains unclear whether BFL wear is associated with an increased risk of the need for surgical correction.

Although unlikely, it is possible that participants treated with BFL spectacles may experience blurry vision, eye discomfort, or impaired depth perception when looking downward through the BFLs when ambulating on foot.

1.4.5 Potential Risks of Single Vision Spectacles

Although unlikely, it is possible that participants treated with single vision spectacles may experience blurry vision and/or eye discomfort. It is also unknown and thus possible that treatment with SVLs alone for ET greater at near may lead to loss of stereoacuity and/or loss of fusion.

1.5 Risks of Examination or Testing Procedures

The procedures in this study are part of daily eye care practice in the United States and pose no known risks. As part of a routine usual-care exam, the participant may receive cycloplegic/dilating eye drops.

1.6 Risk Assessment

There are no risks involved in this study that would not be part of usual care when treating the participants with either SVL or BFL spectacles. The sponsor (Jaeb Center for Health Research) has determined that the protocol's level of risk is consistent with 45 CFR 46.404 and 21 CFR 50.52, which indicates research not involving greater than minimal risk for the individual child involved in the research.

1.7 Summary of Existing Data

Existing studies have failed to demonstrate a benefit of BFLs over SVLs for ET greater at near and, interestingly, some data appear to support the use of SVLs.[19] The Whitman et al study[8] created new uncertainty regarding the benefit of BFLs, in addition to suggesting that BFL wear

may be harmful (i.e., increased likelihood of surgery). Nevertheless, BFLs remain the treatment of choice for most practitioners. In a recent poll of investigators at the recent PEDIG investigator meeting (February 2020) at least 75% of PEDIG care providers use BFLs to treat ET greater at near. There is a pressing need for a randomized clinical trial evaluating the effectiveness of BFLs versus SVLs for ET greater at near.

1.8 Rationale for Present Study

BFLs are commonly used in the treatment of ET greater at near, but their effectiveness is unknown, and has been questioned, particularly since the publication of the study by Whitman and colleagues.[8] BFLs are more costly than SVLs, with a recent study estimating the annual health care expenditures related to BFL treatment in children with ET greater at near, to be $800,000 to $2.8 million in the US alone (2015 data).[8] We are not aware of data that estimate health care expenditures related to subsequently needed treatments and office visits for children with ET greater at near who are not provided BFL treatment.

If SVLs are found to be a superior treatment for ET greater at near, BFL treatment with its related additional costs can be avoided. On the other hand, if BFL treatment is found to be superior to SVLs, this study will have provided the evidence necessary for establishing BFLs as beneficial for reducing the likelihood of motor decompensation and/or for improving binocular alignment and function at near.

In summary, providing reliable evidence of the effectiveness of BFLs versus SVLs for the treatment of ET greater at near would help standardize the currently divergent management practices and enable more efficient utilization of healthcare resources.

1.9 Study Objectives

1. To compare the proportion of participants with failure by 36 months between BFL and SVL groups (failure = worsening of distance ET, reduction in near stereoacuity, frequent diplopia (“more than 2 times per day” over the last week), or undergoing non-study treatment)
2. To compare binocular function scores in BFLs 2 months following failure or at 38 months if no failure (whichever comes first) between the BFL and SVL spectacles groups
3. To compare the proportion of participants with failure by 36 months between BFL and SVL groups according to baseline factor subgroups of: pre-enrollment duration of constant ET, presence of near stereoacuity on the Randot Preschool Stereoacuity test, in-office response of near motor alignment to +3.00 D lenses, and gradient AC/A ratio

1.10 General Considerations

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

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data.

Chapter 2: Study Enrollment and Randomization

2.1 Participant Recruitment and Enrollment

The study plans to enroll up to 444 children for whom informed consent will be obtained. As the recruitment goal approaches completion, sites will be notified of the end date for recruitment into the study. Participants who have signed informed consent forms can be enrolled into the study until the end date, which means the expected recruitment number might be exceeded.

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

2.1.1 Informed Consent

Children with ET who are aged 3 to < 9 years attending ophthalmology or optometry outpatient visits will be identified.

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

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

2.2 Eligibility Criteria

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

- Age 3 to <9 years
- Esodeviation meeting all the following criteria in refractive correction (if required or worn)
    - Constant or intermittent esotropia ≥10Δ measurable by SPCT at near (duration of esotropia sufficient to be measured by SPCT)
    - Distance esotropia (constant, intermittent), esophoria, or orthophoria, with near esodeviation ≥10Δ larger than distance deviation by PACT
        - If constant ET at distance, then must be ≤6Δ by SPCT
        - If intermittent ET or esophoric at distance, can be any magnitude at distance (as long as near esodeviation is ≥10Δ larger than distance deviation by PACT)
- Cycloplegic refraction within past 3 months (but not on day of exam)
- Wearing spectacles if cycloplegic refractive error is 0.75 D SE or more in either eye
- Current spectacles (if worn) must meet the following criteria based on the most recent cycloplegic refraction within 3 months:
    - Worn for at least 4 weeks

- SE refractive error must be corrected within ±0.625 D
- Sphere power must be corrected within ±0.50 D
- Anisometropia must be corrected within ±0.50 D SE
- Cylinder power must be corrected within ±0.50 D
- Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D.

- Best-corrected VA meeting the following criteria:
  - Better-seeing eye VA is age-normal[22, 23]
    - 3 years: 20/50 or better
    - 4 years: 20/40 or better
    - 5-6 years: 20/32 or better
    - 7-12 years: 20/25 or better
  - Worse-seeing eye VA is 20/63 or better
  - IOD in VA within 0.2 logMAR according to conversion shown in Table 1 below:

Table 1: Snellen to LogMAR Conversion

Snellen Equivalent	LogMAR
<20/800	1.7
20/800	1.6
20/640	1.5
20/500	1.4
20/400	1.3
20/320	1.2
20/250	1.1
20/200	1.0
20/160	0.9
20/125	0.8
20/100	0.7
20/80	0.6
20/70	0.55
20/63	0.5
20/60	0.5
20/50	0.4
20/40	0.3
20/32	0.2
20/30	0.2
20/25	0.1
20/20	0.0
20/16	-0.1
20/15	-0.1
20/12	-0.2

Examples for eligibility with respect to Snellen Equivalent and IOD:

- OD = 20/20, OS = 20/30
  - IOD in VA logMAR from Table 1= 0.0 logMAR (20/20) minus 0.2 logMAR (20/30) = -0.2.
    - Because -0.2 logMAR is within 0.2, the participant is **ELIGIBLE**.
- OD = 20/40, OS = 20/70
  - IOD in VA logMAR from Table 1= 0.3 logMAR (20/40) minus 0.55 (20/70) logMAR = -0.25.
    - Because -0.25 is NOT within 0.2, the participant is **NOT ELIGIBLE**.

- Investigator and parent are willing to forgo treatment of ET other than randomized treatment for 38-40 months unless failure criteria are met.
- Investigator is willing to prescribe BFLs only (in both treatment groups) between 36 to 38 months or for 2 months after meeting failure criteria (if failed).

2.3 Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from study participation:

- Previous BFL wear (SVL wear of any duration is allowed)
- Current or planned contact lens wear over the next 3 years
- Myopic refractive error more than -6.00 D SE
- Previous strabismus surgery (including Botox), intraocular surgery (e.g., laser, anti-VEGF injection, or cataract), extraocular surgery (e.g., scleral buckle), or refractive surgery
- Previous amblyopia treatment other than refractive correction within prior 3 months
- Previous treatment for ET using miotics, vision therapy, or prism treatment for ET within prior 3 months
- Vertical deviation ≥3Δ at distance or near by PACT
- Oculomotor findings consistent with infantile ET (e.g., latent nystagmus, manifest nystagmus, DVD)
- AV pattern ≥10Δ difference between upgaze and downgaze by PACT at distance
- Paretic or restrictive strabismus
- Constant exotropia at near during enrollment visit testing through the +3.00 D add (intermittent XT or exophoria allowed)
- Diplopia “more than 2 times per day” over the last week prior to enrollment by parental report. Any report of diplopia must have a frequency of “2 times or less per day” to be eligible.
- Significant developmental delay that would interfere with child’s ability to complete testing
- Neurological condition that could affect ocular motility (e.g., cerebral palsy, Down syndrome)
- Immediate family member (child or sibling) of any investigative site personnel directly affiliated with this study

2.4 Historical Information

Historical information elicited will include the following: date of birth, sex, race, ethnicity, clinical diagnosis, prior esotropia therapy, prior amblyopia therapy, cycloplegic refraction, history of SVL and BFL spectacle wear, and duration of constant ET (if applicable).

2.5 Procedures at Enrollment

The test procedures will be done in the order specified below within 7 days of enrollment through the child's pre-study refractive correction and without cycloplegia. Any spectacle correction worn must meet the criteria specified in section 2.2. For the testing to be performed in trial frames, the two sphere powers should be added and a single lens used for the spherical power component of the trial frames.

1. Lensometry (if wearing spectacles)
2. Diplopia Assessment: Assess diplopia presence and frequency over the last week, by parental report. If present, classify diplopia frequency as "2 times or less per day" or "more than 2 times per day."
3. Monocular Visual Acuity Testing: Distance visual acuity (VA) testing will be performed (right eye first) with the child wearing their spectacles (if worn). Testing method is at investigator discretion, but must meet the following criteria:
    - ATS-HOTV; e-ETDRS; OR crowded single-optotype or single-line HOTV, LEA SYMBOLS, or Snellen letters
        - Allen pictures and Tumbling E's are NOT allowed
    - NOTE: VA testing may instead be performed at the end of the visit
4. Randot Preschool Stereoacuity Test #1: in spectacles at 33 cm* (see *ETS3 Procedures Manual)*
5. Distance Randot Stereoacuity Test: in spectacles at 3 m (see *ETS3 Procedures Manual)*
6. Randot Preschool Stereoacuity Test #2: in trial frames with +3.00 D added lenses at 33 cm* (see *ETS3 Procedures Manual)*
7. Random Dot Butterfly Test: in trial frames with +3.00 D added lenses at 33 cm* (see *ETS3 Procedures Manual)*
8. Preschool Worth 4-Shape Test: in trial frames with +3.00 D added lenses at 33 cm* (see *ETS3 Procedures Manual)*
9. Near Ocular Alignment: in trial frames with +3.00 D added lenses at 33 cm
    - Near alignment will be assessed in trial frames with +3.00 D added lenses by the cover/uncover test, simultaneous prism and cover test (SPCT), and prism and alternate cover test (PACT) in primary gaze at near (1/3 meter) as outlined in the *ETS3 Procedures Manual*.
10. Distance and Near Ocular Alignment Testing:
    - Ocular alignment will be assessed in spectacles by the cover/uncover test, SPCT, and PACT in primary gaze at distance (3 meters) and at near (33 cm) as outlined in the *ETS3 Procedures Manual*.

* Test distance for near stereoacuity and other binocular testing is 33 cm rather than 40 cm because of the focal length of the +3.00 D add

2.6 Spectacle Tolerance Criteria at Enrollment

Spectacles worn at enrollment [whether required (refractive error of 0.75 D or more – see section 2.2) or at investigator discretion] must be worn for 4 or more weeks and must meet the following spectacle tolerance criteria based on lensometry and the cycloplegic refraction performed within the prior 3 months (but not on the day of the exam) which is used to assess eligibility:

- SE refractive error must be corrected within ±0.625 D
- Sphere power must be corrected within ±0.50 D
- Anisometropia must be corrected within ±0.50 D SE
- Cylinder power must be corrected within ±0.50 D
- Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D and within ±5 degrees if cylinder power is >1.00 D

2.7 Randomization

Eligible participants will be randomized 1:1 to the following:

1. Single vision spectacles (SVLs)
2. Bifocal spectacles (BFLs): +3.00 D flat-top bifocal add

The Jaeb Center will construct a separate Master Randomization List using a permuted block design stratified by presence/absence of stereoacuity of at least 960 arcsec or better on the Randot Preschool Stereoacuity Test conducted at near (33 cm) in a trial frame with +3.00 D added lenses.

A child is officially enrolled in the randomized trial when the website randomization process is completed.

2.8 Prescription of Randomized Treatment

Spectacles prescribed at enrollment will be referred to as the **HOME spectacles** for both treatment groups. These are the spectacles that the participants will have at home and be instructed to wear every day for all waking hours (at home, school, outside, etc.).

Single-vision lens (SVL) group:

Participants randomized to treatment with SVLs will be prescribed HOME spectacles meeting the following criteria based on their cycloplegic refraction:

- Full correction of hyperopia/myopia
- Full correction of astigmatism
- Full correction of anisometropia

Children in the SVL group with no refractive error (emmetropia or plano refraction) will be prescribed spectacles with plano lenses.

Bifocal lens (BFL) group:

Participants randomized to treatment with BFLs will be prescribed HOME spectacles meeting the following criteria based on their cycloplegic refraction:

- Full correction of hyperopia/myopia
- Full correction of astigmatism
- Full correction of anisometropia

- +3.00 D bifocal add (flat top, 35 mm with segment height set at mid-pupil - see *ETS3 Manual of Procedures*)
    - Progressive addition lenses (PALs) are NOT allowed to be worn during the study.

Children in the BFL group with no refractive error (emmetropia or plano refraction) will be prescribed spectacles with plano lenses and the +3.00 D bifocal add.

Both treatment groups:
The refractive error correction prescribed at the time of randomization must follow the requirements outlined for each group above. However, if the participant is having problems with blurred vision, then the prescription may be adjusted when the child returns for follow-up as described in section 3.13.2. If the participant develops constant exotropia at near or any type of exodeviation at distance (constant XT, IXT, or exophoria), the prescription may be adjusted as described in section 3.13.3, **AFTER calling one of the Protocol Chairs**.

Participants in both treatment groups (SVLs and BFLs) will also be prescribed a pair of single-vision spectacles to be used for near testing and to facilitate in-office masking of examiners. These spectacles are referred to as the **OFFICE spectacles** and will be sent to the enrolling site where they will be stored on site and used only for testing purposes at study visits (see *ETS3 Manual of Procedures*). The lens power will be +3.00 D more than the full distance correction (i.e., same refractive correction as measured through the BFL add, but made as single-vision spectacles). These OFFICE spectacles will be used for masking purposes during follow-up visits; they will not be sent home with the participant. Throughout the study, any prescription changes that are made to the HOME spectacles for any reason (see sections 3.12.1, 3.13.2 and 3.13.3) will also be made to the OFFICE spectacles at the same time.

Chapter 3: Study Follow-up

3.1 Study Follow-up Visits

Participants randomized in the study generally* will return for follow-up according to the following schedule (timed from randomization, unless otherwise specified):

Protocol-specified Visit/Call	Target Day	Target Window (around target day)	Allowable Window (around target day)
1-month call	Randomization+30 days	± 1 week 23 to 37 days	1 to 76 days
3-month visit	Randomization+91 days	± 2 weeks 77 to 105 days	± 1.5 months 46 to 137 days
6-month visit	Randomization+183 days	± 2 weeks 169 to 197 days	± 1.5 months 138 to 228 days
9-month visit	Randomization+274 days	± 2 weeks 260 to 288 days	± 1.5 months 229 to 320 days
12-month visit	Randomization+365 days	± 2 weeks 351 to 379 days	-1.5 to +3 months 321 to 457 days
18-month visit	Randomization+548 days	± 2 weeks 534 to 562 days	± 3 months 458 to 639 days
24-month visit	Randomization+731 days	± 2 weeks 717 to 745 days	± 3 months 640 to 822 days
30-month visit	Randomization+913 days	± 2 weeks 899 to 927 days	± 3 months 823 to 1004 days
36-month Primary Outcome Visit[b]	Randomization+1096 days	± 2 weeks 1068 to 1124 days	-3 to +6 months 1005 to 1278 days
38-month Secondary Outcome Visit[c,d]	36-month visit +60 days (or 38-months from randomization for confirmed failures occurring before 36 months).	± 4 weeks 32 to 88 days	-1 month to +6.5 months 30 to 258 days from 36-month Visit (from 38 months following randomization for confirmed failures)
Additional if needed	**Target Day**	**Target Window** (around target day)	**Allowable Window (around target day)**
1-month call after new spectacles[e]	Visit at which spectacles changed +30 days	± 1 week 23 to 37 days	1 to 76 days
Failure Confirmation Visit[f]	Visit at which failure criteria met and spectacles updated + 60 days	± 4 weeks 46 to 88 days	30 days to open end (must be completed)
Post-failure Secondary Outcome Visit[g]	Visit at which failure confirmed +60 days	± 4 weeks 32 to 88 days	-1 month to +6.5 months 30 to 258 days from confirmed failure

[b] SVL group is prescribed BFLs at end of the 36-month Primary Outcome Visit. The exception is participants who previously failed, had the post-failure secondary outcome visit, and been released to treatment.

[c] Note that participants who meet failure criteria at 36 months (and have not failed previously) and need their spectacles updated will have a Failure Confirmation Visit 2 months later (4-12 weeks) and return at 40 months for the 38-month Secondary Outcome Visit.

[d] At the 38-month Secondary Outcome Visit, both groups are now in BFLs.

[e] Phone calls from site 1 month ± 1 week from the time spectacles are prescribed or changed (section 3.1.1).

[f] Failure Confirmation Visit: If a participant meets failure criteria at the 12-month visit or later and needs a change in refractive correction, new spectacles will be prescribed, and the participant will return in 4 to 12 weeks to determine (confirm) whether the participant meets failure criteria.

[g] Post-failure Secondary Outcome Visit: If a participant meets failure criteria prior to 36 months, BFLs will be prescribed to the SVL group (BFLs continued in the BFL group) and a Post-failure Secondary Outcome Visit will be scheduled 4 to 12 weeks after the visit at which failure criteria was confirmed (i.e., at a regularly-scheduled study visit or at a separate Failure Confirmation Visit, if one is required).

*Participants who meet confirmed failure criteria (section 3.5) and complete the Post-failure Secondary Outcome Exam will return for the 12- and 24-month follow-up visits (if they have not already been completed) and the 38-month Secondary Outcome Visit as outlined in section 3.7.1; all other remaining visits will be skipped.

3.1.1 Phone Calls

Site personnel will call the parents 1 month ± 1 week following the prescription of any new spectacles or after a change in spectacles. The purpose of the call is to determine whether the new spectacles have been received and are being worn, to determine whether there are any problems / symptoms with wearing the spectacles, and to determine whether the parent has any questions about the study.

3.2 Masking Procedures

Participants will not be masked to their treatment group, given that their spectacles either will or will not have a visible flat-top bifocal. The investigator treating each participant also will not be masked to treatment group. Therefore, an examiner masked to treatment group will measure eye alignment and stereoacuity at all follow-up visits and conduct the binocular function testing at the required follow-up visits. Masking of examiners will be accomplished in two ways. First, unmasked personnel will place painter's tape (provided to sites) over the entire lower half of the HOME spectacle lenses such that the tape covers the entire bottom half and top line of the BFL segment or where the BFL segment would be located (upper edge at mid-pupil) if the SVLs were BFLs (*see ETS3 Procedures Manual*). All distance testing and some near testing will be done through the distance correction using the top portion (above the tape) of the HOME spectacle lenses. Second, where specified, some near testing will be performed with the participant wearing their OFFICE spectacles; these spectacles remain at the study site. Masked exams will be completed at all study visits unless otherwise specified.

3.2.1 Masked Examiner

The masked examiner must be a pediatric optometrist, pediatric ophthalmologist, or certified orthoptist who is not aware of the participant's assigned treatment.

3.3 Follow-up Procedures Prior to 36 Months

The following procedures will be performed in the order specified below at each interim follow-up visit occurring at 3, 6, 9, 12, 18, 24, and 30 months, with participants wearing their HOME spectacles or their OFFICE spectacles as specified by the protocol. Participants who present for a follow-up visit without their HOME spectacles, or whose HOME or OFFICE spectacles do not meet the spectacle tolerance criteria as determined by lensometry (see below) will be tested in trial frames with the appropriate randomized refractive correction (based on the most recent cycloplegic refraction and with any allowed adjustments to the most recent prescription as outlined in sections 3.13.2 and 3.13.3) and either with or without +3.00 D added power (to substitute for OFFICE and HOME spectacles, respectively). The two sphere powers should be added and a single lens used for the spherical power component of the trial frames.

> **NOTE:** Participants with confirmed failure status (sections 3.5 and 3.6) who have completed a Post-failure Secondary Outcome Visit will return for interim follow-up at 12 months and 24 months with abbreviated testing (section 3.7.2).

1. Lensometry:
    - Spectacles (HOME and OFFICE) must meet the following spectacle tolerance criteria as compared with the participant's last prescribed refractive correction (NOTE: if the hyperopic sphere and/or bifocal add power have been reduced per protocol [see sections 3.13.2 and 3.13.3], the sphere and add power must meet the spectacle tolerance criteria as compared with what was last prescribed):
        - SE refraction must be corrected within ±0.625 D
        - Sphere power must be corrected within 0.50 D
        - Anisometropia must be corrected within ±0.50 D SE
        - Cylinder power must be corrected within ±0.50 D
        - Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D, and within ±5 degrees if cylinder power is >1.00 D.
        - If bifocals, bifocal must be a flat-top 35 and meet the following criteria:
            - Height must be within ±2 mm of mid-pupil
            - Power must be within ±0.50 D of that prescribed
            - Total sphere power of the bifocal segment must be corrected within ±0.50 D of the sum of the prescribed bifocal power and distance sphere power
            - Measured bifocal add power (i.e., dioptric difference between distance sphere power and bifocal sphere power) must be within ±0.50 D of prescribed bifocal add power.
    - If at any follow-up visit the participant's spectacles (HOME or OFFICE) do not meet these spectacle tolerance criteria (above) based on the most recent cycloplegic refraction and with allowed adjustments to the most recent prescriptions as outlined in sections 3.13.2 and 3.13.3, then the spectacles must be remade. NOTE that if the spectacles are found to be out of tolerance at any follow-up visit, testing should be performed in trial frames rather than requiring the participant to return for another visit.

2. Diplopia Assessment: Assess diplopia presence and frequency over the last week by parental report. If present, classify diplopia frequency as "2 times or less per day" or "more than 2 times per day."
3. Monocular Visual Acuity Testing: Distance VA will be measured (right eye first) with the participant wearing their HOME spectacles and without cycloplegia, using the same test method used at enrollment.
    - ATS-HOTV; e-ETDRS; OR crowded single-optotype or single-line HOTV, LEA SYMBOLS, or Snellen letters (Allen pictures and Tumbling E optotypes are NOT allowed)
    - NOTE: VA testing may be performed at the end of the visit.
4. Randot Preschool Stereoacuity Test with OFFICE spectacles #1 **(masked)**:
    - Tested in OFFICE spectacles at 33 cm (see *ETS3 Procedures Manual*)
5. Ocular Alignment Testing – cover/uncover test, SPCT, and PACT **(masked):**
    - Wearing OFFICE spectacles and testing at near (33 cm) only
    - Wearing HOME spectacles with participant viewing **through the TOP** of the lenses (with bottom half of lenses taped) at both distance (3 m) and near (33 cm) (see *ETS3 Procedures Manual*) *
6. Randot Preschool Stereoacuity Test in OFFICE spectacles #2 **(masked)**:
    - Tested a second time in OFFICE spectacles at 33 cm.*
7. Additional Testing: if failure criteria are met (section 3.5) **(masked)**
8. Cycloplegic Refraction (at all 12-, 24-, and 30-month visits, and only if failure is met at any other visit):
    - NOTE: If failure criteria are met, the additional procedures in section 3.5.1 must be completed prior to the cycloplegic refraction.
    - The cycloplegic refraction must be performed 30 to 45 minutes following at least one application of cyclopentolate 1%.
    - If the cycloplegic refraction reveals uncorrected refractive error outside the spectacle tolerance criteria (above), the spectacle correction must be updated (see section 3.12). (Smaller refractive changes may be prescribed at investigator discretion). Any changes that are made to the HOME spectacles will be made to the OFFICE spectacles at the same time.

*Test distance for near stereoacuity and other binocular testing is 33 cm rather than 40 cm because of the focal length of the +3.00 D add

3.4 36-Month Primary Outcome Visit

At the 36-month primary outcome visit, participants will complete the following test procedures in the order specified below (1-9) while wearing their HOME spectacles or OFFICE spectacles, as specified. Participants who present without their HOME spectacles or whose HOME or OFFICE spectacles do not meet the spectacle tolerance criteria (section 3.12) as determined by lensometry, should be tested in trial frames. The trial lenses should be the appropriate randomized refractive correction (based on the most recent cycloplegic refraction and with the allowed adjustments to the most recent prescriptions as outlined in sections 3.13.2 and 3.13.3) either with or without the added +3.00 D power to substitute for the OFFICE and HOME spectacles, respectively. The two sphere powers should be added and a single lens used for the spherical power component of the trial frames.

1. Lensometry (HOME and OFFICE spectacles)
2. Diplopia Assessment: Assess diplopia presence and frequency over the last week by parental report. If present, classify diplopia frequency as "2 times or less per day" or "more than 2 times per day."
3. Monocular Visual Acuity Testing: Distance VA will be measured (right eye first) with the participant wearing their HOME spectacles and without cycloplegia, using the same test method used at enrollment.
4. Randot Preschool Stereoacuity Test wearing OFFICE spectacles #1 **(masked)**: Tested in OFFICE spectacles at 33 cm (see *ETS3 Procedures Manual)*.*
5. Random Dot Stereo Butterfly Test wearing OFFICE spectacles **(masked)**: Tested in OFFICE spectacles at 33 cm (see *ETS3 Procedures Manual)*.*
6. Preschool Worth 4-Shape test wearing OFFICE spectacles **(masked)**: Tested in OFFICE spectacles using the hand-held Preschool Worth 4-Shape test held at 33 cm (see *ETS3 Procedures Manual)*.*
7. Randot Preschool Stereoacuity Test wearing OFFICE spectacles #2 **(masked)**: tested in OFFICE spectacles at 33 cm (see *ETS3 Procedures Manual*)*
8. Ocular Alignment Testing - cover/uncover test, SPCT, and PACT **(masked)**:
   - Wearing OFFICE spectacles and testing at near (33 cm) only
   - Wearing HOME spectacles with participant viewing **through the TOP** of the lenses (with bottom half of lenses taped) at both distance (3 m) and near (33 cm) (see *ETS3 Procedures Manual*)
9. Distance Randot Stereotest (**masked**): tested **through TOP** of HOME spectacles at 3 m (with bottom half taped)
10. Randot Preschool Stereoacuity Test wearing HOME spectacles **(masked)**: Tested in HOME spectacles with participant viewing **through the TOP** of the lenses at 33 cm* (with bottom half of lenses taped; see *ETS3 Procedures Manual*)*

*Test distance for near stereoacuity and other binocular testing is 33 cm rather than 40 cm because of the focal length of the +3.00 D add

NOTE: Participants who meet confirmed failure criteria (section 3.5) and complete the Post-failure Secondary Outcome Exam do not complete the 36-month visit.

3.4.1 Prescribing Bifocal Spectacles at the 36-month Primary Outcome Visit

For participants who HAVE NOT failed prior to or by the end of the 36-month Primary Outcome Visit:

- Participants in the SVL group will be prescribed BFLs to be worn until the 38-month Secondary Outcome Visit.
- Participants in the BVL group will continue to wear BFLs until the 38-month Secondary Outcome Visit.

For participants who FAIL AT the 36-month Primary Outcome Visit:

- SVL participants who meet CONFIRMED failure criteria at the 36-month visit (i.e., fail and do not require a change in spectacles) will be prescribed BFLs to be worn until the 38-month Secondary Outcome Visit.
- BFL participants who meet CONFIRMED failure criteria at the 36-month visit (i.e., fail and do not require a change in spectacles) will continue to wear their BFLs until the 38-month Secondary Outcome Visit.
- Participants in both treatment groups who meet failure criteria at the 36-month visit and require a Failure Confirmation Visit (see section 3.6) because their spectacles are NOT within study tolerance will be prescribed updated spectacles according to their respective treatment group and return for a Failure Confirmation Visit.

BFL spectacles that are being prescribed per protocol at the 36-month Primary Outcome Visit (as opposed to being prescribed at investigator discretion) should meet the following criteria based on the participant's most recent cycloplegic refraction:

- Full correction of hyperopia/myopia
- Full correction of astigmatism
- Full correction of anisometropia
- +3.00 D bifocal add (flat top, 35 mm, segment height set mid-pupil, see *ETS3 Manual of Procedures*).
- Children with no refractive error (emmetropia or plano refraction) will be prescribed spectacles with plano lenses and the +3.00 D bifocal add.

Progressive addition lenses (PALs) are NOT allowed during the study. SVL participants will wear their newly prescribed BFL spectacles until their 38-month Secondary Outcome Visit.

Regardless of the correction worn, all participants return for the 38-month Secondary Outcome Visit.

3.5 Failure Criteria

Treatment failure is defined as meeting one or more of the following criteria at any follow-up visit between 3 months to 36 months inclusive:

1. Constant ET ≥15Δ by SPCT at distance. (NOTE: intermittent ET and esophoria of any magnitude are NOT considered failures).
2. Decrease in near stereoacuity on the Randot Preschool Stereoacuity Test (at 33 cm) of 2 or more levels from baseline (see levels below) stereo or from 960" (equivalent to 800" when measured at 40 cm) at baseline to nil (*criteria not applicable if nil near stereo at baseline)*
   - Baseline stereoacuity is defined as the near stereoacuity performed with +3.00 D added to the participant's enrollment distance spectacle correction in trial frames.
   - At all follow-up visits, the best of two stereo measures in the OFFICE lenses will be used to determine treatment failure.
   - Stereoacuity values are calculated for the 33 cm test distance required for testing through the added +3.00 D lenses at near (instead of the standard 40 cm). **NOTE:** Participants without measurable near stereoacuity at baseline cannot fail by stereoacuity criteria.

Table 2. Baseline and Follow-up Randot Preschool Stereoacuity Test Levels for Defining Treatment Failure

Baseline Stereoacuity (in trial frames with lens power that is +3.00D more than distance correction)[a]	Follow-up Stereoacuity for Treatment Failure (best of two tests in OFFICE spectacles)
48” (40” at 40 cm)	120” or worse
72” (60” at 40 cm)	240” or worse
120” (100” at 40 cm)	480” or worse
240” (200” at 40 cm)	960” or worse
480” (400” at 40 cm)	Nil
960” (800” at 40 cm)	Nil
Nil	Not applicable

[a]The two sphere powers should be added and a single lens used for the spherical power component of the trial frames.

3. Binocular diplopia with a frequency of “more than 2 times per day” over the last week by parental report.
4. If any nonsurgical or surgical treatment for ET other than the randomized treatment is started before the participant meets failure criteria, the participant will be considered a failure at the visit at which the non-randomized treatment is prescribed.

If treatment failure occurs, proceed according to whether the participant failed PRIOR to the 36-month Primary Outcome Visit (section 3.5.1) or AT the 36-month Primary Outcome Visit (section 3.5.2).

If failure has been CONFIRMED previously in the study, there is no need to confirm failure at subsequent visits. Participants with previously CONFIRMED failure will continue in follow-up as outlined in section 3.7.1 regardless of whether they meet failure criteria again on subsequent visits.

3.5.1 Procedures for Participants Meeting Failure Criteria at a Study Visit PRIOR to the 36-month Primary Outcome Visit

All participants who meet failure criteria PRIOR to the 36-month Primary Outcome Visit will undergo the following **additional** testing in the order specified below (1-5) at the visit when the failure criterion is met:

1. Random Dot Stereo Butterfly test **(masked)**: tested in OFFICE spectacles at 33 cm.*
2. Preschool Worth 4-Shape test **(masked)**: tested in OFFICE spectacles at 33 cm.*
3. Distance Randot Stereotest **(masked)**: tested through **TOP** of HOME spectacles at 3 meters (with bottom half of lenses taped). (See *ETS3 Procedures Manual* for taping instructions)
4. Randot Preschool Stereoacuity Test **(masked)**: tested through **TOP** of HOME spectacles at 33 cm (with bottom half of lenses taped) (*See ETS3 Procedures Manual*)*
5. Cycloplegic Refraction (after the testing above is completed)

- The cycloplegic refraction must be performed 30 to 45 minutes following at least one application of cyclopentolate 1%.
- If the cycloplegic refraction reveals that the spectacles no longer meet the spectacle tolerance criteria according to section 3.12, the spectacle correction must be updated (both HOME and OFFICE spectacles).

*Test distance for near stereoacuity and other binocular testing is 33 cm rather than 40 cm because of the focal length of the +3.00 D add.

If based on the cycloplegic refraction performed at this visit:

- The spectacle correction IS within tolerance (section 3.12) and does not need to be updated:
  1. Failure is CONFIRMED at this visit.
  2. The participant should be prescribed BFLs (if in the SVL group) or continued in BFLs (if in the BFL group) (section 2.8)
  3. The participant should return in 2 months (window: 4 to 12 weeks) for their Post-failure Secondary Outcome Visit (section 3.7).

- The spectacle correction is NOT within tolerance (section 3.12) and needs to be updated:
  1. Failure is NOT CONFIRMED at this visit.
  2. The participant should be prescribed new spectacles (according to the criteria in section 2.8) consistent with the participant's randomized group assignment to SVL or BFL spectacles.
  3. The participant will return for a Failure Confirmation Visit (section 3.6) in 2 months (window: 4 to 12 weeks).

3.5.2 Procedures for Participants Meeting Failure Criteria AT the 36-month Primary Outcome Visit

All participants who meet failure criteria AT the 36-month visit must have a cycloplegic refraction at the end of this study visit (after eye alignment, stereoacuity, and other binocular function testing, etc.):

- The cycloplegic refraction must be performed 30 to 45 minutes following at least one application of cyclopentolate 1%.
- If cycloplegic refraction reveals that the spectacles are no longer within the spectacle tolerance criteria according to section 3.12, then both HOME and OFFICE spectacle corrections must be updated.

NOTE: All eye alignment, stereoacuity, and other binocular function testing must already have been completed as part of the 36-month Primary Outcome visit (for all participants) before instilling cyclopentolate drops.

If the spectacle correction IS within tolerance (section 3.12) and does not need to be updated:

1. Failure is CONFIRMED at this 36-month visit.
2. SVL group participants should be prescribed BFLs and BFL group participants continued in BFLs (section 3.4.1)
3. Both groups should return in 2 months (window: 4 to 12 weeks) for their 38-month Secondary Outcome Visit (section 3.8).

If the spectacle correction is NOT within tolerance (section 3.12) and needs to be updated:

1. Failure is NOT CONFIRMED at this 36-month visit.
2. Participants should be prescribed new spectacles (according to the criteria in section 2.8) consistent with their randomized group assignment.
3. Participants should return for a Failure Confirmation Visit in 2 months (window: 4 weeks to 12 weeks).
4. Regardless of whether study failure criteria are confirmed or not confirmed at the Failure Confirmation Visit, all SVL participants will be prescribed BFLs and all BFL participants will continue with BFL wear (section 3.4.1).
5. Both groups return in 2 months (window: 4 to 12 weeks) following the Failure Confirmation Visit for their 38-month Secondary Outcome Visit. In this specific situation, the 38-month Secondary Outcome Visit will be scheduled at 40 months after randomization (section 3.8).

3.6 Failure Confirmation Visit

Failure Confirmation Visits occur 2 months (window: 4 to 12 weeks) after suspected failures that occurred for participants who were found to need a change in spectacles at that time. The purpose of the Failure Confirmation Visit is to determine whether failure criteria are met after the participant has been wearing the updated randomized treatment spectacles. Note that meeting *any* failure criteria in updated spectacles will be considered a CONFIRMED failure. It is not required that the participant fail the same criterion that was initially failed before the spectacles were updated (e.g., could have failed distance motor criterion initially but now fails near stereo criterion; this is still failure).

> **NOTE:** The Failure Confirmation Visit (if required) is not allowed to be missed regardless of timing. If the timing of the Failure Confirmation Visit overlaps with a subsequent follow-up visit, the Failure Confirmation Visit must be completed *in lieu of* the follow-up visit (or *before* the 38-month visit). Regardless of whether any regularly scheduled follow-up visits have been missed, the Failure Confirmation Visit must be completed when the participant returns at the next study visit.

All testing in section 3.4 (same as 36-month Primary Outcome Visit) must be repeated at the Failure Confirmation Visit, with participants wearing their HOME spectacles or OFFICE spectacles (or appropriate trial frames) as specified.

- If failure criteria are NOT CONFIRMED at a Failure Confirmation Visit occurring **before** the 36-month visit, no changes are made to treatment and the participant continues with the next scheduled follow-up visit for which the participant is not currently in the window, regardless of how soon.

- If failure criteria are NOT CONFIRMED at a Failure Confirmation Visit occurring **after** the 36-month Primary Outcome Visit, participants will:
  - Be prescribed BFLs (if in SVL group) or continued in BFLs (if in the BFL group) (section 3.4.1)
  - Return in 2 months (window: 4 to 12 weeks) for their 38-month Secondary Outcome Visit (section 3.8).

- If failure criteria are CONFIRMED at **ANY** Failure Confirmation Visit (regardless of timing), participants will:
  - Be prescribed BFLs if in the SVL group or continued in BFLs if in the BFL group (section 3.4.1)
  - Return in 2 months (window: 4 to 12 weeks) for their:
    - Post-failure Secondary Outcome Visit (section 3.7) if failure occurred prior to the 36-month Primary Outcome Visit or
    - 38-month Secondary Outcome Visit if failure occurred at the 36-month Primary Outcome Visit (section 3.8).

3.7 Post-failure Secondary Outcome Visit (After Confirmed Failure)

Post-failure Secondary Outcome Visits occur 2 months (window: 4 to 12 weeks) after a CONFIRMED failure at either a protocol-specified visit or a Failure Confirmation Visit. All testing procedures completed at the 38-month Secondary Outcome Visit (section 3.8) will be completed at this Post-failure Secondary Outcome Visit.

After a Post-failure Secondary Outcome Visit is completed:

- Further treatment is at investigator discretion (including whether to continue BFL or SVL spectacles).

3.7.1 Treatment After the Post-failure Secondary Outcome Visit

Participants with confirmed failure status (sections 3.5 and 3.6) who have completed a Post-failure Secondary Outcome Visit prior to 36 months may be prescribed treatment at investigator discretion. Note that office spectacles will no longer be prescribed.

3.7.2 Follow-up After the Post-failure Secondary Outcome Visit

Participants with confirmed failure status (sections 3.5 and 3.6) who have completed a Post-failure Secondary Outcome Visit prior to 36 months will return for follow-up at 12 months and 24 months (with reduced testing as described below), and for the 38-month Secondary Outcome Visit (as described in section 3.8); all other study visits will be skipped.

At the 12- and 24-month visits, these participants will undergo the following (reduced) testing while wearing their habitual correction:

1. Monocular Visual Acuity Testing: Distance VA will be measured (right eye first) with the participant wearing habitual correction and without cycloplegia, using the same test method used at enrollment.
   - ATS-HOTV; e-ETDRS; OR crowded single-optotype or single-line HOTV, LEA SYMBOLS, or Snellen letters (Allen pictures and Tumbling E optotypes are NOT allowed)
   - NOTE: VA testing may be performed at the end of the visit.
2. Randot Preschool Stereoacuity Test with habitual correction
   - Tested in habitual correction at 33 cm (see *ETS3 Procedures Manual*)*
3. Ocular Alignment Testing – cover/uncover test, SPCT, and PACT**:**
   - Wearing habitual correction at both distance (3 m) and near (33 cm) (see *ETS3 Procedures Manual*)*
4. Cycloplegic Refraction (required only if not completed within the past 12 months):

- The cycloplegic refraction must be performed 30 to 45 minutes following at least one application of cyclopentolate 1%.
  If the cycloplegic refraction reveals uncorrected refractive error, spectacle changes may be prescribed at investigator discretion.

3.8 38-month Secondary Outcome Visit

All participants will complete a 38-month Secondary Outcome Visit, including participants who had a Post-failure Secondary Outcome Visit earlier in the study. The 38-month Secondary Outcome Visits will occur at one of the following times:

- 2 months (±4 weeks) after the 36-month Primary Outcome Visit if:
  - failure has not been met by 36 months, OR
  - failure is met at 36 months and does not require confirmation
- 2 months (±4 weeks) after the Failure Confirmation Visit (40 months) following failure which requires confirmation at the 36-month Primary Outcome Visit
- At 38 months (±4 weeks) after randomization if failure was confirmed prior to 36 months

At the 38-month Secondary Outcome Visit, most participants will be wearing HOME spectacles that will be bifocals; however, some participants who have previously met failure criteria may not be wearing BFLs. A cover/uncover test at near will be performed for participants who are not wearing BFLs to determine whether they have esotropia (see test procedure #5); if esotropia is present, then +3.00D lenses will be required for near testing (except for the second Randot Preschool Stereotest measure, which is performed through the distance correction only). If any participant presents to the visit without their HOME spectacles (if prescribed) or if the spectacles do not meet the spectacle tolerance criteria as determined by lensometry, trial frames will be used for testing.

The following test procedures are to be performed <u>in the order specified below</u>; procedures 4-9 must be performed by an examiner masked <u>to original treatment assignment</u>:

1. Lensometry (HOME spectacles)
2. <u>Diplopia Assessment</u>: Assess diplopia presence and frequency over the last week, by parental report. If present, classify diplopia frequency as “2 times or less per day” or “more than 2 times per day.”
3. <u>Monocular VA Testing</u>: through TOP of HOME spectacles (if wearing)

Items 4-10 will be performed by an examiner masked to original treatment assignment (SVLs or BFLs); most participants are measured in a BFL lens correction at this visit (unless previously released to treatment at investigator discretion).

4. <u>Distance Randot Stereotest</u>: through TOP of HOME spectacles (if wearing) at 3 m **(masked)**
5. <u>Cover/uncover test at near (**for participants NOT currently wearing BFLs)** to determine the optical correction</u> to be used for Randot Preschool Stereoacuity #1, Randot Butterfly, Worth 4-Shape, and ocular alignment at near (cover/uncover, SPCT, and PACT testing) (tests #6, 7, 8 and 10 below):

- Perform a cover/uncover test at near through the HOME spectacles (or without spectacles, if none were prescribed)
- If an esotropia is present on the cover/uncover test at near, the specified testing must be completed in either 1) +3.00 lenses placed in Halberg or Janelli clips attached to the HOME spectacles or 2) a trial frame with a lens power that is +3.00D more than the HOME spectacles.
- If no esotropia is present on the cover/uncover test at near, the specified testing must be completed through the HOME spectacles (or without spectacles, if none were prescribed).

6. Randot Preschool Stereoacuity Test #1: through BOTTOM of HOME spectacles if currently wearing BFLs (otherwise, see step #5) at 33 cm* **(masked)**
7. Random Dot Stereo Butterfly test: through BOTTOM of HOME spectacles if currently wearing BFLs; (otherwise, see step #5) at 33 cm* **(masked)**
8. Preschool Worth 4-Shape test: through BOTTOM of HOME spectacles if currently wearing BFLs (otherwise, see step #5) at 33 cm* **(masked)**.
9. Randot Preschool Stereoacuity Test #2: through TOP of HOME spectacles for at 33 cm* **(masked)**
10. Ocular Alignment Testing: in HOME spectacles **(masked)**
    - Cover/uncover test, SPCT, and PACT at 3 m through TOP of HOME spectacles
    - Cover/uncover test, SPCT, and PACT through BOTTOM of HOME spectacles if currently wearing BFLs (otherwise, see step #5)

*Test distance for near stereoacuity/binocularity testing is 33 cm rather than 40 cm because of the focal length of the +3.00 D add.

Study follow-up will end for all participants after the 38-month Secondary Outcome Visit is completed.

3.9 Inability to Complete a Study Visit

If a child is not sufficiently cooperative (for any reason) for valid study data to be collected at a study visit, the child may return for continuation of the study visit on another day. This visit should be scheduled within 10 days or before the end of the study-visit window, whichever is sooner. The decision to have the child return on a subsequent day must be made by the masked examiner prior to the end of the masked exam. Any test procedures or measurements in question because of participant fatigue will be repeated at the return visit (all testing does not need to be repeated).

If the participant's family does not have sufficient time to complete a study visit and must leave prior to completing all required study testing (e.g., not able to stay for a cycloplegic refraction when meeting failure criteria), the participant must be brought back to complete testing within 10 days or before the end of the study-visit window, whichever is sooner.

3.10 Initiating Non-randomized Treatment for Esotropia (ET)

Non-randomized treatment for ET is NOT permitted during the study unless the following 3 conditions have been met:

1. Participant has met failure criteria (section 3.5)

2. Failure was confirmed either at the initial visit (section 3.5) or at the Failure Confirmation Visit (section 3.6)
3. Participant has completed their Post-failure Secondary Outcome Visit (section 3.7).

If none of the failure criteria are met but the participant is experiencing overwhelming social concerns or significant symptoms (*other than frequent or constant diplopia at distance or near, which is a failure criterion)* associated specifically with the ET, the investigator **must call one of the Protocol Chairs** to discuss the case and obtain approval for an exception prior to initiating any non-randomized treatment for ET.

To the extent possible, participants for whom non-study treatment is planned (after discussion with Protocol Chair) should proceed as if one of the three protocol-specified failure criteria were met. Thus, they should complete the additional testing in section 3.5.1 (including the cycloplegic refraction) and a Post-failure Secondary Outcome Visit (section 3.7) prior to initiating any non-study treatment. The SVL participants will be prescribed BFL spectacles to be worn prior to the Post-failure Secondary Outcome Visit and the BFL participants should continue wearing BFLs.

3.11 Treatment of Amblyopia

Patching, Bangerter foils, and binocular treatment for amblyopia are allowed at investigator discretion during the study. However, atropine and other cycloplegic drops, and/or bifocal lenses prescribed for treating amblyopia are not allowed.

3.12 Spectacle Tolerance Criteria for Follow-up

The following spectacle tolerance criteria will apply throughout the study (unless previously released to treatment at investigator discretion):

a. Spectacles (HOME and OFFICE) must meet the following spectacle tolerance criteria as compared with the participant's most recent cycloplegic refraction (NOTE: if hyperopic sphere and/or the bifocal add power has been reduced per protocol, sphere and add power must be within tolerance of what was prescribed):
   - SE refraction must be corrected within ±0.625 D
   - Sphere power must be corrected within ±0.50 D
   - Anisometropia must be corrected within ±0.50 D SE
   - Cylinder power must be corrected within ±0.50 D
   - Cylinder axis must be within ±10 degrees if cylinder power is ≤1.00 D, and within ±5 degrees if cylinder power is >1.00 D.
   - Bifocal must be a flat-top 35 and meet the following tolerance criteria:
     - Height must be within ±2 mm of mid-pupil
     - Power must be within ±0.50 D of that prescribed
     - Total sphere power of the bifocal segment must be corrected within ± 0.50 D of the sum of the prescribed bifocal power and distance sphere power
     - Measured bifocal add power (lensometry difference between distance sphere power and bifocal sphere power) must be within ±0.50 D of prescribed bifocal add power

3.12.1 Change in Spectacles Because Lensometry Reveals Spectacles are Out of Tolerance

When lensometry reveals that the spectacles do not meet spectacle tolerance criteria (section 3.12) based on the most recent spectacle prescription (which includes any reduction in hyperopic sphere and bifocal add power) and the most recent cycloplegic refraction, the spectacles must be remade.

3.13 Management of Refractive Error During Follow-up

3.13.1 Change in Spectacles Following a Change in Cycloplegic Refraction

If a cycloplegic refraction during follow-up reveals a change in refractive error such that the current spectacles do not correct the refractive error to within spectacle tolerance criteria (section 3.12) then both HOME and OFFICE spectacle corrections must be updated (new lenses prescribed).

The new spectacles must be prescribed based on the most recent cycloplegic refraction and the full correction for hyperopia, myopia, and astigmatism is to be prescribed. Those randomized to the BFL group also will be prescribed a +3.00 D add.

- NOTE: No reduction in hyperopic correction or bifocal add is permitted when initially prescribing required new spectacles during follow-up; however, a reduction in hyperopic correction or bifocal add can be made at a subsequent visit, if warranted (see sections 3.13.2 and 3.13.3).

3.13.2 Reduction of Hyperopic Correction Because of Distance Blur

The initial study spectacles will be prescribed with the full-plus hyperopic correction. However, if one of the following occurs at any time during follow-up, the investigator may reduce the distance hyperopic correction (sphere) symmetrically by 0.25 D or 0.50 D from the original randomized prescription. Hyperopic correction may be reduced if the participant:

(1) has a decrease in VA of 0.2 logMAR or more (based on conversion of Snellen equivalent to logMAR. (See Table 1 in section 2.2),
(2) complains of distance blur (even if VA has not decreased), or
(3) resists wearing the spectacles and the investigator believes the resistance may be from an inability to relax accommodation fully

3.13.3 Management of Refractive Error to Control Exodeviations

If at any time during follow-up a participant develops a constant exotropia at NEAR, the investigator should determine the amount of reduced hyperopic correction in the reading portion of the lens (bifocal add for the BFL group and spherical component of the entire lens for the SVL group) necessary to reduce the frequency of the exotropia such that it is no longer constant AND **contact one of the Protocol Chairs** prior to making any changes.

If at any time during follow-up the child develops an exodeviation at DISTANCE (constant, intermittent, or phoria), the investigator should determine the amount of reduced hyperopic correction necessary to reduce the exodeviation to ortho or a small amount of esodeviation AND **contact one of the Protocol Chairs** prior to making any changes.

Chapter 4: Testing Procedures and Questionnaires

4.1 Clinical Assessments

The following test procedures as described in the *ETS3 Procedures Manual* will be completed for both treatment groups at each visit as specified by the protocol.

1. Monocular Visual Acuity Testing: Monocular distance VA will be tested in both eyes with the participant wearing their study-specified spectacle correction. The right eye is tested, with the left eye occluded with an adhesive patch. The left eye is tested after the right eye. The testing method is at investigator discretion provided the following are used: ATS-HOTV; e-ETDRS protocol; OR crowded single-optotype or single-line HOTV, LEA SYMBOLS or Snellen letters. (Allen pictures and tumbling E optotypes are NOT allowed). Testing does not need to be performed by a study-certified tester and it is not required to be measured on a PEDIG-certified VA testing system, but the chart used needs to be appropriately calibrated. The same testing method must be used throughout the study. Testing time for both eyes typically is in the range of 5 to 7 minutes.

2. Lensometry: The distance correction and the bifocal add (where applicable) will be measured. Measurement time takes between 1 and 3 minutes and does not involve the participant.

3. Randot Preschool Stereoacuity Test: The Randot Preschool Stereoacuity Test measures 6 levels (40 to 800 arcsec) of stereoacuity at near (40 cm). Corresponding levels range from 48 to 960 arcsec when tested at 33 cm. The test consists of 3 booklets, each designed to test 2 levels of stereoacuity, and each level consisting of 4 panels, 3 of which contain a random dot stereogram. The participant wears polarized lenses over their spectacle correction. The examiner asks the participant if they can identify a specific black and white shape in the booklet and then asks the participant to point to the panel containing the corresponding stereogram image, as outlined in the *ETS3 Procedures Manual*. The test must be administered by a certified examiner. Testing time is approximately 2-4 minutes.

4. Distance Randot Stereotest: The Distance Randot Stereotest measures 4 levels (60, 100, 200, and 400 arcsec) of stereoacuity at 3 meters. The test consists of a booklet designed to display 2 pages at a time, each page containing a panel with a single random dot stereogram. The participant wears polarized lenses over their spectacle correction and identifies the stereogram images they see, as outlined in the *ETS3 Procedures Manual*. The test must be administered by a certified examiner. Testing time is approximately 2-4 minutes.

5. Random Dot Stereo Butterfly Test: The Random Dot Stereo Butterfly Test measures 2000 arcsec of stereoacuity at 40 cm (2400 arcsec at 33 cm). The test consists of a booklet with a single stereogram of a butterfly. The participant wears polarized lenses over their spectacle correction and is asked to pinch the tip of the butterfly's wings, which will appear to float off the page if the participant has stereoacuity. The test must be administered by a certified examiner. Testing time is approximately 1-2 minutes.

6. Preschool Worth 4-Shape Test: The Preschool Worth-4-Shape test is used to assess a participant's second-degree sensory fusion. The test utilizes a flashlight with 4 back-lit

shapes: red heart, green circle, green moon, and white star. The participant views the shapes at approximately 33 cm while wearing red/green filter glasses and identifies the shapes that are seen as outlined in the *ETS3 Procedures Manual.* The test can determine whether the participant has second-degree fusion, suppression, or diplopia. The test must be administered by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist. Testing time is approximately 3-5 minutes.

7. Ocular Alignment Testing:
   Ocular alignment will be assessed by the cover/uncover test, simultaneous prism and cover test (SPCT), and the prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (33 cm) as outlined in the *ETS3 Procedures Manual*. Testing must be done by a pediatric ophthalmologist, pediatric optometrist, or certified orthoptist. Testing time is approximately 3-5 minutes.

8. Cycloplegic Refraction: The cycloplegic refraction must be/have been performed 30 to 45 minutes following at least one application of cyclopentolate 1%. The cycloplegic refraction may be done with spectacles off or as an over-refraction in front of the spectacles. Subjective refinement is allowed. Testing time is approximately 1-5 minutes (following 30-45 minutes of waiting for the cycloplegic drops to take effect).

The following information will be collected by interviewing the parent(s):

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

Chapter 5: Unanticipated Problem and Adverse Event Reporting

5.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center on an eCRF all unanticipated problems meeting the criteria below. Sites must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all three (3) of the following criteria:

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

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

5.2 Adverse Events

5.2.1 Reportable Adverse Events

Because study treatment with bifocal or single-vision spectacles is non-invasive and consistent with usual care, it is not expected that there would be any significant adverse events other than those already being captured as part of clinical outcome assessments (e.g., treatment failure criteria). For this reason, only serious, related adverse events shall be reported to the Coordinating Center, on the applicable eCRF, within seven (7) days of identification. Furthermore, investigators must still abide by IRB reporting requirements. If covered by the JCHR IRB, investigators are required to report all serious, related adverse events to the JCHR IRB within seven (7) calendar days of identification of the event.

5.3 Safety Oversight

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

The objective of the DSMC review is to decide whether the study (or study treatment for an individual or study cohort) should continue per protocol, proceed with caution, be further

investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site, or for the entire study) is a potential outcome of a DSMC safety review.

5.4 Stopping Criteria

The study may be discontinued by the Steering Committee (with approval of DSMC) prior to the preplanned completion of follow-up for all study participants. No formal guidelines for stopping the study for futility or efficacy are pre-specified (section 7.4).

5.5 Participant Discontinuation of Study Treatment

Rules for discontinuing study treatment use are one of the following:

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

Even if the study treatment is discontinued, the participant will be encouraged to remain in the study through the 38-month Secondary Outcome Visit.

Chapter 6: Miscellaneous Considerations

6.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided the parents' contact information. The Jaeb Center may contact the parents of the participants. Permission for such contacts will be included in the Informed Consent Form. The principal purpose of the contacts will be to develop and maintain rapport with the participant's family and to help coordinate the scheduling of study visits, when needed.

6.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

6.3 Cost of Spectacles

Spectacles required as part of the study will be paid for by the study. Spectacle changes are required following a cycloplegic refraction that indicates the spectacles are out of study tolerance limits, at the time of failure for children in the SVL group, and at the 36-month Primary Outcome Visit for the SVL group. Spectacles may be updated and paid for by the study whenever a spectacle change is required or made at investigator discretion for both treatment groups. Spectacles may be replaced and paid for by the study if in poor condition (e.g., significantly scratched lenses, broken frame) at any time during follow-up.

At the parent's request, a separate prescription for SVL sports glasses may be provided for wear during sports. Sports glasses will not be paid for by the study. Sports glasses must only be worn when playing sports.

6.4 Participant Withdrawal

Participation in the study is voluntary and a participant may withdraw at any time. For participants who withdraw, their data collected prior to their withdrawal will be used. This stipulation is specified in the consent form.

6.5 Confidentiality

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

Chapter 7: Statistical Considerations

7.1 Statistical and Analytical Plans

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

7.2 Primary Objective and Hypothesis

The primary objective is to determine if participants with ET greater at near who are prescribed SVLs and BFLs have different failure probabilities by 36 months.

The primary outcome is treatment failure by 36 months, defined as meeting any one of the following criteria at any follow-up visit from 3 months to 36 months inclusive:

1. Constant ET ≥15Δ by SPCT at distance. (NOTE: intermittent ET and esophoria of any magnitude are NOT considered failures.)
2. Decrease in near stereoacuity on the Randot Preschool Stereoacuity (RPS) Test of 2 or more levels from baseline, or from 960" at baseline to nil (see Table 2 in section 3.5 for reference).
    - At follow-up visits, the best of two stereoacuity measures in OFFICE spectacles will be used.
    - Baseline stereoacuity is defined as the near stereoacuity recorded with +3.00 D power added to the participant's enrollment distance spectacle correction in trial frames.
    - Approximately 50% of participants are expected to have nil near stereoacuity at baseline; it is acknowledged that these participants will not be able to meet the near stereoacuity failure criteria.
3. Binocular diplopia with a frequency of "more than 2 times per day" over the last week at distance or near, by parental report.

If nonsurgical or surgical treatment for ET other than the randomized treatment is before meeting failure criteria, that participant will be considered a failure at the visit that such treatment is prescribed.

The study is designed as a superiority study to evaluate a 2-sided primary null hypothesis that the failure probability by 36 months is the same between the SVL and BFL groups versus the alternative hypothesis that it is different:

$$\mathbf{H_{null}} \quad BFL_{\%\text{ of failure by 36 months}} = SVL_{\%\text{ of failure by 36 months}}$$

$$\mathbf{H_{alternative}} \quad BFL_{\%\text{ of failure by 36 months}} \neq SVL_{\%\text{ of failure by 36 months}}$$

The composition of the treatment failures (i.e., whether due to distance motor failure, near stereoacuity failure, or diplopia "more than 2 times per day" over the last week) is also of primary interest. However, the failure criteria may be interrelated and thus there is no specific hypothesis for each criterion.

7.3 Sample Size

Sample size estimation is based on data from the retrospective cohort study conducted by Whitman et al.[24] After approximately 4 years of follow-up, 15.6% of the BFL group and 3.9% of

the SVL group underwent strabismus surgery, all of whom had an increase in the distance angle of deviation to more than 10Δ by PACT (average increase from baseline was 25Δ in the BFL group and 20.5Δ in the SVL group). In the current study, the primary outcome is based on distance motor failure (based on SPCT), near stereoacuity failure, or diplopia "more than 2 times per day" over the last week by 36 months. Given a shorter follow-up, the proportion of distance motor failures may be less than that found in the Whitman et al. study. The proportion of near stereoacuity failures is believed to be less in the BFL group than the SVL group, but no data are available to provide estimates of the failure proportion for each group.

Table 4 shows the sample size estimates under various assumptions for the primary outcome in the SVL group and the difference in the primary outcome between the BFL and SVL groups. To be conservative, the total sample size needed to detect a treatment group difference is calculated using a two-sided Pearson chi-square test with a type I error rate of 5% and 90% power. Power is expected to increase slightly using a time-to-event approach for the primary outcome analysis.

Table 4. Total sample size needed to detect a treatment group difference in proportions of failure by 36 months under various assumptions

% of Failure in SVL Group	Treatment Group Difference in % of Failures (BFL – SVL)							
	5%	6%	7%	8%	9%	10%	15%	20%
3%	870	656	518	424	356	306	172	116
4%	1018	756	592	480	400	342	186	124
5%	1164	856	664	534	442	376	202	130
6%	1304	954	734	588	484	408	214	138
7%	1442	1140	802	640	524	440	228	146
8%	1576	1140	870	690	564	472	242	152
9%	1708	1230	936	740	602	502	254	158
10%	1836	1318	998	788	640	532	266	164
11%	1960	1402	1060	834	676	562	278	172
12%	2082	1486	1120	880	712	590	290	178
13%	2198	1566	1178	924	746	618	302	182
14%	2314	1644	1236	966	780	644	312	188
15%	2424	1720	1290	1008	812	670	322	194

Assuming a failure probability of 5% in the SVL group and 15% in the BFL group, a sample size of 376 (188 per group) provides 90% power to detect a treatment group difference with a two-sided type I error rate of 5%. The total sample size is increased to 444 (222 per group) to account for up to a 15% loss to follow-up over 36 months.

7.4 Interim Monitoring

An interim sample size re-estimation based on 12-month treatment failure outcome was considered because of uncertainty in the assumed proportions of failure by 36 months in the

treatment groups. However, it is unclear how well the 12-month outcome will predict the 36-month outcome. Because of this additional uncertainty, this approach will likely increase the bias in the estimation of the 36-month primary outcome. To minimize this bias, sample size re-estimation would have to be performed based on the partial 36-month outcome data, but it would be too late to affect recruitment since recruitment is expected to be completed within 3 years. In addition, the estimated total sample size of 444 is close to the maximum number of eligible participants that could potentially be recruited. Therefore, a sample size re-estimation will not be performed.

Interim monitoring for futility and/or efficacy was also considered. For the same reasons, interim monitoring would have to be conducted based on the partial 36-month outcome data when recruitment is likely completed. Even if there is evidence for futility and/or efficacy for the primary outcome at that time, the remaining follow-up visits would likely be continued to collect data on all the outcomes including binocular function at 38 months. Therefore, there will be no formal guidelines for stopping the trial for futility or efficacy. The DSMC will review safety and efficacy data periodically.

7.5 Analysis Dataset

The primary efficacy analysis will follow an intent-to-treat (ITT) principle. All randomized participants will be included in the primary analysis dataset and analyzed according to the group they were originally assigned, regardless of what treatment (if any) they received.

7.6 Analysis of Primary Outcome – Treatment Failure by 36 Months

There may be participants who are lost to follow-up before their 36-month primary outcome data are collected. To use the data collected from these participants before they are lost to follow-up, a time-to-event analysis will be performed for the primary outcome. For participants who meet failure criteria before or at the 36-month Primary Outcome Visit, time to treatment failure will be defined as the time from randomization to the visit at which the failure is confirmed (either at the initial visit or later at a Failure Confirmation Visit because the spectacle correction must be updated [section 3.6]). If a participant is prescribed non-randomized treatment for ET before meeting failure criteria, they will be considered a failure at the time when such treatment is prescribed. Participants lost to follow-up are considered censored at the time of their last recorded visit. If a participant is lost to follow-up before failure is confirmed, they will be censored at their last visit for the primary analysis.

The hazard ratio of treatment failure for treatment with BFLs versus SVLs and a two-sided 95% confidence interval (CI) will be estimated with a Cox proportional hazards model. The model will be adjusted for baseline near stereoacuity by the Randot Preschool Stereotest (RPS) in +3.00 D trial frames and baseline magnitude of the distance esodeviation by SPCT. The treatment group difference in the probability of failure and a two-sided 95% CI will be estimated using the direct adjustment method. The proportional hazards and functional form assumptions will be evaluated.

The timing and composition of failures (distance motor, near stereoacuity, diplopia, starting non-protocol treatment) will be tabulated by treatment group to aid in the interpretation of the treatment group difference for failure probability by 36 months.

7.6.1 Sensitivity Analyses for Primary Outcome

As a sensitivity analysis, if a participant meets the failure criteria prior to a required spectacle update but is lost to follow-up before the failure is confirmed, the participant will be treated as a failure at the time when they initially met the failure criteria (suspected failure). The primary analysis will be repeated with these unconfirmed failures being counted as failures.

As an additional sensitivity analysis, treatment crossovers (BFL group participants who have bifocals formally discontinued and begin to wear SVL; SVL group participants prescribed bifocals) that occur before meeting any of the clinical measures for failure will be censored at the visit date when treatment crossover occurred.

7.6.2 Contingency Plan for Primary Outcome

If the assumptions for the Cox model are not satisfied, an exact logistic regression model with the same covariates will be attempted. If the adjusted model fails to converge, a model will be fit without the adjustment for covariates. If the exact logistic regression still fails to converge, Barnard's exact test will be performed.

7.7 Analysis of Secondary Outcomes

7.7.1 Binocular Function Test Score in BFLs at the Secondary Outcome Visit

A secondary outcome is the binocular function test score at the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed). The test score is assigned on an ordinal scale that combines the results of the RPS test, Random Dot Stereo Butterfly test, and Preschool Worth 4-shape (W4S) test that were measured using the bottom portion of the participants' BFLs. Given that BFLs can potentially reduce the magnitude of near ET, which might in turn improve near stereoacuity, it was felt critical to measure binocular function after a period of BFL wear in both treatment groups. Consequently, after 36 months of SVL or BFL wear, the SVL group will be prescribed BFLs, the BFL group will continue wearing their BFLs, and both groups will be re-assessed at the 38-month Secondary Outcome Visit. Because participants who meet failure criteria for the primary outcome at a prior visit must be released to treatment at investigator discretion, these participants will be prescribed BFLs (if in the SVL group) or continue in BFL (if in the BFL group) and return within 2 months after meeting failure criteria for a Post-failure Secondary Outcome Visit.

The possible levels of binocular function will be 48, 72, 120, 240, 480, 960 arcsec (RPS test), 2400 arcsec (Random Dot Stereo Butterfly test), and 10,000 or 100,000 arcsec (fusion or suppression, respectively, indicated by Preschool W4S test). The binocular function test score will be calculated by converting binocular function to a log value ranging from 1.68 (log of 48 arcsec) to 5.0 (log of 100,000 arcsec). Baseline near stereoacuity on the RPS test that was measured through +3.00 D lenses will be used in the calculation of the binocular function test score at baseline, and the Random Dot Stereo Butterfly and Preschool W4S tests that were also measured through +3.00 lenses. The score at the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed) and the change from baseline will be tabulated for each treatment group. A treatment group comparison of the scores will be performed using the exact Wilcoxon rank sum test to determine whether the treatment groups have different distributions of the score. If the hypothesis test for the primary outcome is significant, an alpha of 0.05 will be passed down to this test. If not, this outcome will be exploratory with no *P*-value reported.

7.7.2 Treatment Effects on Failure by 36 Months by Subgroup

This study has liberal inclusion/exclusion criteria. It is possible that the treatment effect is not consistent across different subgroups of the population. With potentially small numbers of participants in subgroups, results of subgroup analyses will be interpreted with caution and the interpretation may depend on whether the primary analysis demonstrates a significant overall treatment group difference.

The subgroup analyses will be performed by modifying the primary analysis to adjust for the subgroup factor and an interaction between the subgroup factor and treatment group.

Baseline subgroups of interest are:

1. Duration of ET prior to enrollment: <6 months vs. ≥ 6 months
2. Stereoacuity
    a. Distance Randot Stereotest: nil vs. not nil
    b. Near RPS Test through +3.00 D lenses: nil vs. not nil
3. Intermittent ET (or esophoria) vs. constant ET
4. Motor response at near to +3.00 D trial frames testing classified as follows:
    a. No response (tropia ≥10Δ by SPCT)
    b. Microtropia (<10Δ)
    c. Phoria or orthophoria
5. Near stereoacuity response vs. no near stereo response through +3.00 D trial frames
    a. Stereoacuity response is defined as near stereoacuity improvement of at least 2 levels (for participants who have stereoacuity in SVLs) or presence (any level) of near stereoacuity in +3.00 D lenses (for participants who do not have stereoacuity in SVLs).
    b. Participants who have 48” or 72” of near stereopsis in SVLs cannot meet the stereoacuity response criteria and will be excluded from this subgroup analysis
6. Gradient AC/A ratio
    a. By tertiles
    b. <2.5 vs. 2.5 to 6 vs. >6
7. Age: 3 to <6 years vs. 6 to <9 years

The proportion of participants that fall into each of the subgroups is unknown. Table 5 shows the expected half-width of the 95% CI for the treatment group difference in the primary outcome in subgroups of various sizes. For example, if the observed proportions of failure by 36 months are 5% with SVLs and 15% with BFLs in a subgroup with 100 participants per treatment group, the expected half-width of the 95% CI for the treatment group difference would be 8%.

Table 5. Expected half-width of 95% CI* for treatment group difference in the proportion of failures by 36 months in subgroups with various sizes

Observed % of Failure in SVL Group (p1)	Observed % of Failure in BFL Group (p2)	Observed Treatment Difference in % of Failure (p2 – p1)	Number Per Treatment Group in Subgroup							
			25	50	75	100	125	150	175	200
5%	5%	0%	12%	9%	7%	6%	5%	5%	5%	4%
5%	10%	5%	15%	10%	8%	7%	7%	6%	5%	5%
5%	15%	10%	16%	12%	9%	8%	7%	7%	6%	6%
5%	20%	15%	18%	13%	10%	9%	8%	7%	7%	6%
5%	25%	20%	19%	13%	11%	10%	8%	8%	7%	7%
10%	10%	0%	17%	12%	10%	8%	7%	7%	6%	6%
10%	15%	5%	18%	13%	11%	9%	8%	7%	7%	6%
10%	20%	10%	20%	14%	11%	10%	9%	8%	7%	7%
10%	25%	15%	21%	15%	12%	10%	9%	8%	8%	7%
10%	30%	20%	21%	15%	12%	11%	10%	9%	8%	8%
15%	15%	0%	20%	14%	11%	10%	9%	8%	7%	7%
15%	20%	5%	21%	15%	12%	11%	9%	9%	8%	7%
15%	25%	10%	22%	16%	13%	11%	10%	9%	8%	8%
15%	30%	15%	23%	16%	13%	11%	10%	9%	9%	8%
15%	35%	20%	23%	17%	13%	12%	10%	10%	9%	8%

*Half-width of a 2-sided 95% CI = 1.96*sqrt[p1*(1-p1)/n1 + p2*(1-p2)/n2]

7.8 Exploratory Analysis of Tertiary Outcomes

All tertiary outcomes will be considered exploratory. Point estimates and 95% CIs for treatment group differences will be reported (where applicable) with no adjustment for multiplicity. Binocularity and stereoacuity outcomes that are better suited to non-parametric methods will be described using the median and interquartile range for each treatment group.

7.8.1 Ocular Alignment at Distance and Near

7.8.1.1 Comparison of Randomized Treatments at 36 Months or Confirmed Failure

At the time of the primary outcome (36 months or confirmed failure), the magnitude of deviation by PACT and the change from baseline will be tabulated and described with summary statistics for each treatment group. The treatment group difference in the magnitude of deviation and the 95% CI will be estimated using an analysis of covariance (ANCOVA) adjusting for the baseline PACT magnitude.

The magnitude of deviation by SPCT and the change from baseline will also be tabulated and described with summary statistics for each treatment group. The proportions with constant ET of ≥10Δ, constant ET of <10Δ, intermittent ET, esophoria, and orthophoria will be tabulated by treatment group.

The above analyses will be performed separately for distance and near deviations as measured through distance correction, to assess the magnitude of the underlying angle of deviation. In addition, the near deviations as measured through OFFICE spectacles (i.e., SVLs with cycloplegic refraction and +3.00 D power) will be analyzed similarly, to assess the impact of +3.00 D lenses on the near deviation.

7.8.2 Binocular Function Test Score

7.8.2.1 Subgroup Analysis of Secondary Outcome Binocular Function Score

The secondary outcome of binocular function test score in BFLs at the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed) as defined in section 7.7.1 will be further evaluated in subgroups specified in section 7.7.2.

7.8.2.2 Comparison of Overall Treatment Strategies at 38 Months

To evaluate real-world effectiveness of the overall treatment strategies the binocular function test score at the 38-month Secondary Outcome Visit and the change from baseline will be tabulated by treatment group. Distinct from the secondary outcome binocular function score (sections 7.7 and 7.8.2.1), this analysis will utilize the 38-month data for all participants, regardless of whether they met failure criteria at a prior visit. Scores will be calculated using the same algorithm as described in section 7.7.1 for combining the results of the RPS, Random Dot Butterfly, and W4S tests that are measured through the bottom of the HOME spectacles for most participants (see section 3.8 for exceptions). Results of the individual tests will also be tabulated separately for each treatment group.

7.8.2.3 Comparison of Randomized Treatments at 36 Months or Confirmed Failure

The binocular function score will be evaluated at the primary outcome (36 months or prior failure) (before the BFLs are prescribed) and compared between the SVL group and the BFL group. At these visits, the best of two near stereoacuity measures by the RPS test in OFFICE spectacles will be used when calculating the binocular function score. The binocular function score at the time of treatment failure (if failed) or the 36-month Primary Outcome Visit (if not failed) and the change from baseline will be tabulated by treatment group.

7.8.3 Near Stereoacuity

At baseline, near RPS stereoacuity measured in +3.00 D trial frames will be used for analysis. At regular follow-up visits between 3 months and 36 months, the best of the two RPS measures in OFFICE spectacles will be used for analysis.

7.8.3.1 Comparison of Randomized Treatments at the Secondary Outcome Visit

Near stereoacuity measured using the bottom portion of the participants' BFLs at the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed) and the change from baseline will be tabulated for each treatment group.

7.8.3.2 Comparison of Overall Treatment Strategies at 38 Months

To evaluate real-world effectiveness of the overall treatment strategies, near RPS stereoacuity at the 38-month Secondary Outcome Visit and the change from baseline will be tabulated for each treatment group, regardless of whether failure criteria were met at a prior visit. The analysis will

use the same RPS stereoacuity measurement (in arcsec) that is taken through the bottom of the HOME spectacles for most participants (see section 3.8 for exceptions).

7.8.3.3 Comparison of Randomized Treatments at 36 Months or Confirmed Failure

Near RPS stereoacuity at the time of the primary outcome (36 months or prior failure) and the change from baseline will be tabulated for each treatment group.

7.8.4 Distance Stereoacuity

Scores from the Distance Randot Stereotest will be collected at enrollment, at 36 months using the top portion of the HOME spectacles, and at 38 months using the top portion of the BFLs. Distance stereoacuity will also be measured if a failure criterion is met before the 36-month visit.

7.8.4.1 Comparison of Randomized Treatments at the Secondary Outcome Visit

The Distance Randot Stereotest measured in BFLs at the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed) and the change from baseline will be tabulated for each treatment group.

7.8.4.2 Comparison of Overall Treatment Strategies at 38 Months

To evaluate real-world effectiveness of the overall treatment strategies, distance stereoacuity at the 38-month Secondary Outcome Visit and the change from baseline will be tabulated for each treatment group, regardless of whether failure criteria were met at a prior visit.

7.8.4.3 Comparison of Randomized Treatment at 36 Months or Confirmed Failure

The Distance Randot Stereotest measured at the time of the primary outcome (36 months or confirmed failure) and the change from baseline will be tabulated for each treatment group using the participant's HOME spectacles.

7.8.5 Short-term Effect of BFLs in SVL Group Post-failure and at 38 Months

In the SVL group, the changes in near RPS stereoacuity, distance stereoacuity, and the binocular function test score from the time of the primary outcome (36 months or confirmed failure) to the Secondary Outcome Visit (Post-failure Secondary Outcome visit if failed or 38-month Secondary Outcome Visit if not failed) will be tabulated and described with summary statistics to evaluate the short-term effect of BFL wear.

7.9 Safety Analyses

7.9.1 Distance Motor and Near Stereoacuity Treatment Failures

The occurrences of distance motor failure and near stereoacuity failure, as each is defined under "treatment failure" (section 7.2) will be tabulated for each treatment group as safety outcomes.

The risk of undergoing strabismus surgery is not included as a safety outcome given that surgery is at the discretion of the investigator provided failure criteria have been met, with biases expected to vary considerably among investigators.

7.9.2 Diplopia

Any new cases of diplopia will be tabulated for each treatment group. In addition, diplopia occurring "more than 2 times per day" over the last week will also be tabulated for each treatment group.

7.9.3 Reduction of Distance Visual Acuity

Any cases of inter-ocular difference not within 0.2 logMAR and reduced visual acuity in best refractive correction (≥0.2 logMAR) in either eye will be tabulated by treatment group.

7.10 Spectacle Adherence

Spectacle adherence assessed by a parental estimate at the start of each visit will be tabulated over time for each treatment group over the 36 months in the study. Separately, spectacle adherence for each treatment group will be tabulated for the 36- to 38-month window for non-failures, and for the time window from prior treatment failure (i.e., Failure Confirmation Visit, if required; otherwise, from the failure visit) to the Post-failure Secondary Outcome Visit if failed.

7.11 Additional Tabulations and Analyses

The following tabulations and analyses will be performed:

- A flow chart accounting for all participants according to treatment group for all visits
- Visit completion rates for each follow-up visit according to treatment group
- Baseline demographics and clinical characteristics overall and by treatment group at randomization
- Protocol deviations according to treatment group
- Number of and reasons for non-study treatment according to treatment group

Chapter 8: Data Collection and Monitoring

8.1 Case Report Forms and Other Data Collection

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

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

8.2 Study Records Retention

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

8.3 Quality Assurance and Monitoring

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

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

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

Elements of the RBM may include:

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

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

8.4 Protocol Deviations

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

The site PI, protocol PI (if different) and all study staff are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 9: Ethics/Protection of Human Participants

9.1 Ethical Standard

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

9.2 Institutional Review Boards

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

9.3 Informed Consent Process

9.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout that individual's study participation. Written IRB-approved consent materials and consent discussions must be in a language understandable to the participants and their parent(s). For example, if the parent(s) primary language is Spanish, then the Spanish consent form, as well as other participant/parent facing materials (e.g., questionnaires) must be in Spanish. Also, the use of a translator approved by the Coordinating Center is required to support not only the consent process, but also the participants and their parent(s) understanding and communication for the duration of the study.

Extensive discussion of risks and possible benefits of participation will be provided to participants and their families. Consent forms will be approved by the IRB and the parent/legal guardian will be asked to read and review the document. The investigator will explain the research study to the parent and participant and answer any questions that may arise. All parents and participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Parents and participants (old enough to sign per IRB) will have the opportunity to carefully review the written consent form and ask questions prior to signing.

Parents should have the opportunity to discuss the study with their partner or family physician or think about it prior to agreeing to participate. Written informed consent will be obtained from a parent and written or verbal assent from the child (depending on age and IRB requirements) prior to performing any study-specific procedures that are not part of the child's routine care. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the family for their records. The rights and welfare of the participants will be protected by emphasizing to them and their parent(s) that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological

samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or study data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

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

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

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

9.3.3 Future Use of Data

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

Chapter 10: References

1. Greenberg AE, Mohney BG, Diehl NN, Burke JP. Incidence and types of childhood esotropia: a population-based study. *Ophthalmology* 2007;114:170-174.
2. Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of amblyopia and strabismus in African American and Hispanic children ages 6 to 72 months. The Multi-ethnic Pediatric Eye Disease Study. *Ophthalmology* 2008;115:1229-1236.
3. Friedman DS, Repka MX, Katz J, et al. Prevalence of amblyopia and strabismus in white and African American children aged 6 through 71 months. The Baltimore Pediatric Eye Disease Study. *Ophthalmology* 2009;116:2128-2134.
4. McKean-Cowdin R, Cotter SA, Tarczy-Hornoch K, et al. Prevalence of amblyopia or strabismus in Asian and non-Hispanic white preschool children: Multi-ethnic Pediatric Eye Disease Study. *Ophthalmology* 2013;120:2117-2124.
5. Duane A. *A New Classification of the Motor Anomalies of the Eye. Based Upon Physiological Principles, Together with their Symptoms, Diagnosis and Treatment. The Prize Assay of the Alumni Association of the College of Physicians and Surgeons, New York for 1896*. New York: J. H. Vail; 1897.
6. Burke JP. Distance-near disparity esotropia: can we shrink the gap? *Eye (Lond)* 2015;29:208-213.
7. Fresina M, Schiavi C, Campos EC. Do bifocals reduce accommodative amplitude in convergence excess esotropia? *Graefes Arch Clin Exp Ophthalmol* 2010;248:1501-1505.
8. Whitman MC, MacNeill K, Hunter DG. Bifocals fail to improve stereopsis outcomes in high AC/A accommodative esotropia. *Ophthalmology* 2016;123:690-696.
9. Olitsky SE. High AC/A ratio esotropia: do we really need to be using bifocals? *Am Orthopt J* 2016;66:5-9.
10. Vivian AJ, Lyons CJ, Burke J. Controversy in the management of convergence excess esotropia. *Br J Ophthalmol* 2002;86:923-929.
11. Arnoldi KA. Convergence excess: characteristics and treatment. *Am Orthopt J* 1999;49:37-47.
12. Garretty T. Convergence excess accommodative esotropia: A descriptive review of patients presenting over a period of 10 years. *Br Ir Orthopt J* 2011;8:23-28.
13. Pratt-Johnson JA, Tillson G. The management of esotropia with high AC/A ratio (convergence excess). *J Pediatr Ophthalmol Strabismus* 1985;22:238-242.
14. Arnoldi K, Shainberg M. High AC/A ET: Bifocals? surgery? or nothing at all? *Am Orthopt J* 2005;55:62-75.
15. von Noorden GK, Avilla CW. Nonaccommodative convergence excess. *Am J Ophthalmol* 1986;101:70-73.
16. Parks MM. Abnormal accommodative convergence in squint. *AMA Arch Ophthalmol* 1958;59:364-380.
17. Pratt-Johnson JA, Tillson G. Sensory outcome with nonsurgical management of esotropia with convergence excess (a high accommodative convergence/accommodation ratio). *Can J Ophthalmol* 1984;19:220-223.
18. American Academy of Ophthalmology Pediatric Ophthalmology/Strabismus Panel. *Esotropia and exotropia preferred practice pattern*. San Francisco, CA: American Academy of Ophthalmology; 2017:Available at: http://www.aao.org/ppp.

19. Gerling A, Arnoldi K. Single-vision lenses: a comparison of management of high AC/A esotropia and refractive esotropia. *Strabismus* 2013;21:106-109.
20. Ludwig IH, Parks MM, Getson PR. Long-term results of bifocal therapy for accommodative esotropia. *J Pediatr Ophthalmol Strabismus* 1989;26:264-270.
21. von Noorden GK, Morris J, Edelman P. Efficacy of bifocals in the treatment of accommodative esotropia. *Am J Ophthalmol* 1978;85:830-834.
22. Drover JR, Felius J, Cheng CS, Morale SE, Wyatt L, Birch EE. Normative pediatric visual acuity using single surrounded HOTV optotypes on the Electronic Visual Acuity Tester following the Amblyopia Treatment Study protocol. *J AAPOS* 2008;12:145-149.
23. Pan Y, Tarczy-Hornoch K, Cotter SA, et al. Visual acuity norms in pre-school children: the Multi-Ethnic Pediatric Eye Disease Study. *Optom Vis Sci* 2009;86:607-612.
24. Whitman MC, MacNeill K, Hunter DG. Bifocals fail to improve stereopsis outcomes in high AC/A accommodative esotropia. *Ophthalmology* 2016;123:690-696.