Signature Page

AMBLYOPIA TREATMENT STUDY

A Randomized Trial of Dichoptic Treatment for Amblyopia in Children 8 to 12 Years of Age

Protocol Identifying Number: ATS24

Version Number: 1.0

29 April 2024

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	R. Kraker	R. Henderson	29Apr2024	

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ANCOVA	Analysis of covariance
ATS	Amblyopia Treatment Study
BCVA	Best corrected visual acuity
CI	Confidence interval
CFR	Code of Federal Regulations
CRF	Case report form
D	Diopter
DHHS	Department of Health and Human Services
DSMC	Data safety and monitoring committee
eCRF	Electronic case report form
E-ETDRS	Electronic-Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good clinical practice
ICH	International Council for Harmonisation
IOD	Interocular difference
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
logMAR	Logarithm of the minimal angle of resolution
NIH	National Institutes of Health
ODM	Occlusion dose monitor
PACT	Prism and alternate cover test
PedEyeQ	Pediatric Eye Questionnaire
PEDIG	Pediatric Eye Disease Investigator Group
QA	Quality assurance
QC	Quality control
RBM	Risk based monitoring
RCT	Randomized clinical trial
SAP	Statistical Analysis Plan
SPCT	Simultaneous prism and cover test
VA	Visual Acuity

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Randomized Trial of Dichoptic Treatment for Amblyopia in Children 8 to 12 Years of Age.
Précis	In older children, standard amblyopia treatments appear to be less effective, and many children have residual amblyopia after treatment. Dichoptic technology provides a more immersive and engaging treatment environment which may result in improved adherence and greater treatment benefit. However, dichoptic treatments have not been studied in older children with amblyopia. This study will evaluate two dichoptic treatments to determine effectiveness over continued optical correction alone in older children with amblyopia.
Investigational Devices	Luminopia digital and Vivid Vision digital therapeutic systems.
Primary Objectives	To formally compare the effectiveness of Luminopia 1 hour / day, 6 days per week while wearing optical correction if needed versus continued optical correction alone if needed, in children 8 to 12 years of age, as a superiority test. To formally compare the effectiveness of Vivid Vision 25 minutes / day, 6 days per week while wearing optical correction if needed versus continued optical correction alone if needed, in children 8 to 12 years of age, as a superiority test. If both Luminopia and Vivid Vision are superior to continued optical correction alone if needed, then the effectiveness of Luminopia versus Vivid Vision will be formally compared in children 8 to 12 years of age, as a superiority test. If either Luminopia or Vivid Vision is NOT superior to continued optical correction alone if needed, then the treatment group difference and 95% CI for the difference between treatment groups will be calculated with no p-value and the results will be considered exploratory only. It is noted for the comparison of Luminopia versus Vivid Vision, the absence of a statistically significant difference cannot rule out the presence of a clinically meaningful difference between active treatment groups. The test is powered assuming a difference between treatments as small as 3.75 letters with a standard deviation of 7.0 letters
Study Design	Multicenter, randomized clinical trial.
Number of Sites	The study is open to all clinical sites approved to participate in the PEDIG network.
Endpoints	Primary Efficacy Outcome: • Change in amblyopic eye logMAR distance VA between randomization and 18 weeks. Key Secondary Efficacy Outcomes: • Functional Vision, Social, and Frustration/Worry quality of life domains as measured by the Pediatric Eye Questionnaire (PedEyeQ). Key Safety Outcomes: • Change in fellow eye logMAR distance VA between randomization and 18 weeks. • Proportion of participants with no strabismus who develop a new strabismus. • Proportion of participants with strabismus who develop a worsening strabismus ≥10Δ. • Proportion of participants with parental report of diplopia more than once per week. • Proportion of participants reporting headache, eyestrain, nausea, seizures, dizziness, increase in frequency of night terrors, or skin irritation.
Population	**Key Inclusion Criteria:** • Age 8 to 12 years. • Amblyopia associated with anisometropia, strabismus (<=5Δ at distance and near measured by SPCT), or both.

PARTICIPANT AREA	DESCRIPTION

	• VA, measured in each eye without cycloplegia in current refractive correction (if applicable) using the E-ETDRS VA protocol on a study-approved device displaying single surrounded optotypes, as follows:
	  o VA in the amblyopic eye 20/40 to 20/200 inclusive (33 to 72 letters with E-ETDRS).
	  o VA in the fellow eye 20/25 or better (≥ 78 letters with E-ETDRS).
	  o Interocular difference ≥ 3 logMAR lines (≥ 15 letters), i.e., amblyopic eye VA at least 3 logMAR lines worse than fellow eye VA.
	• Spectacles/contact lens correction (if needed) worn for at least 18 weeks, or until stability of VA is demonstrated (<1-line [5-letter] change by the same testing method measured on 2 exams at least 9 weeks apart).
	• Interpupillary distance of 52mm to 72mm inclusive.
	• No treatment with cycloplegic eyedrops (e.g., atropine) in the last 2 weeks.
	• No more than 2 weeks (cumulative) prior dichoptic treatment.
	• No diplopia by parental report (defined as no more than once per week).
	• No myopia greater than -6.00D SE in either eye.

Sample Size	252 accounting for lost to follow-up (84 in each treatment group)
Phase	Phase III Randomized Clinical Trial
Treatment Groups	Random assignment (1:1:1) to: • Luminopia Group: dichoptic movies/shows wearing the Luminopia headset prescribed 1 hour per day (treatment time can be split into shorter sessions totaling 1 hour each day) 6 days a week with current optical correction if needed • Vivid Vision Group: dichoptic games using the Vivid Vision headset, prescribed approximately 25 minutes per day (treatment time to complete the day's sessions can be split into shorter sessions totaling about 25 minutes each day) 6 days per week with current optical correction if needed • Continued Optical Correction Group: continued full-time optical correction alone if needed
Participant Duration	If randomized, participation in the study will last 36 weeks or less.
Study Duration	Thirty-five (35) months from first enrollment to last participant visit (26 months to recruit, followed by 9 months of follow up).
Protocol Overview/Synopsis	Participants eligible for the study will be randomly allocated (1:1:1) to receive either Luminopia dichoptic treatment while wearing optical correction if needed, Vivid Vision dichoptic treatment while wearing optical correction if needed, or continued optical correction alone if needed, with clinical assessments at 9- and 18-weeks post-randomization. At the 18-week primary outcome visit, participants who were randomly assigned to receive optical correction alone if needed with an IOD of 1 logMAR line (5 letters) or more, will be offered randomization to Luminopia or Vivid Vision dichoptic therapy and if they accept, followed forward with visits at 27- and 36-weeks post-randomization. The study will end for all other participants at 18 weeks.

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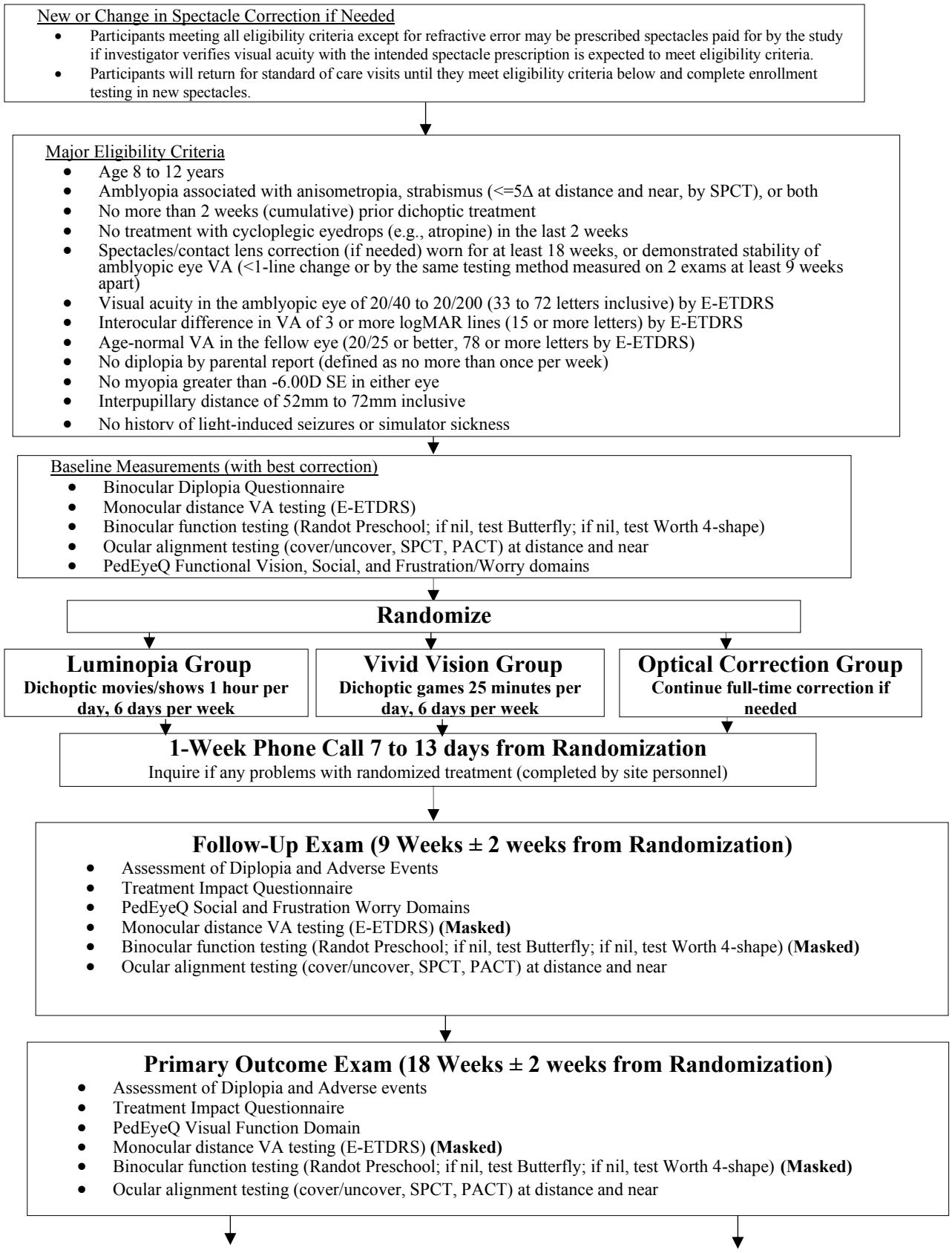
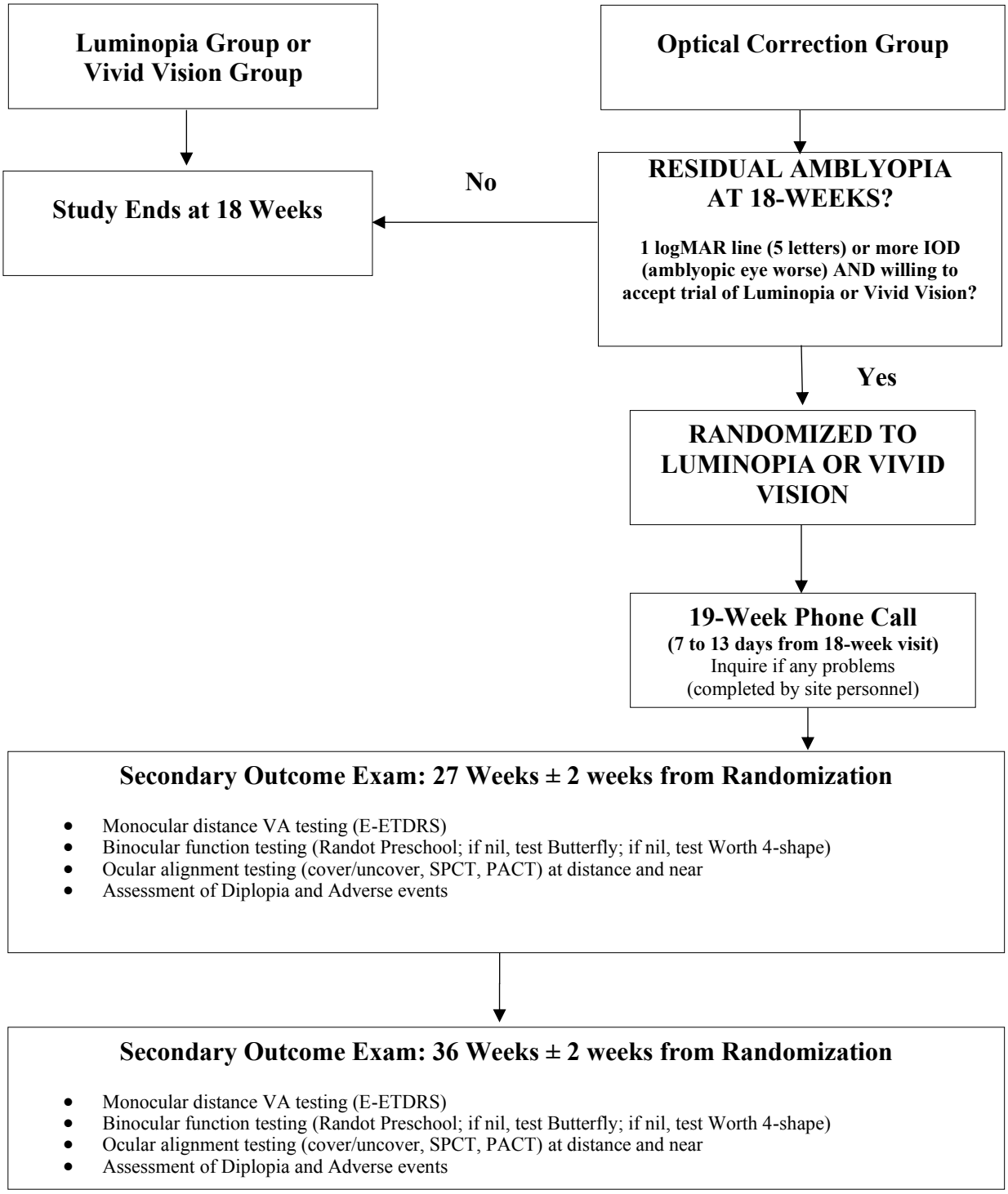
STUDY SUMMARY FLOW CHART




Luminopia Group or Vivid Vision Group
Optical Correction Group
RESIDUAL AMBLYOPIA AT 18-WEEKS?
1 logMAR line (5 letters) or more IOD (amblyopic eye worse) AND willing to accept trial of Luminopia or Vivid Vision?
No
Study Ends at 18 Weeks
Yes
RANDOMIZED TO LUMINOPIA OR VIVID VISION
19-Week Phone Call
(7 to 13 days from 18-week visit)
Inquire if any problems
(completed by site personnel)
Secondary Outcome Exam: 27 Weeks ± 2 weeks from Randomization
Monocular distance VA testing (E-ETDRS)
Binocular function testing (Randot Preschool; if nil, test Butterfly; if nil, test Worth 4-shape)
Ocular alignment testing (cover/uncover, SPCT, PACT) at distance and near
Assessment of Diplopia and Adverse events
Secondary Outcome Exam: 36 Weeks ± 2 weeks from Randomization
Monocular distance VA testing (E-ETDRS)
Binocular function testing (Randot Preschool; if nil, test Butterfly; if nil, test Worth 4-shape)
Ocular alignment testing (cover/uncover, SPCT, PACT) at distance and near
Assessment of Diplopia and Adverse events

SCHEDULE OF STUDY VISITS AND PROCEDURES

Visit	Informed Consent (and Assent if required)	Demographics / Medical History	Distance VA	Binocular Function Testing	Ocular Alignment	PedEyeQ Functional Vision	PedEyeQ Social/Frustration/Worry	Binocular Diplopia Questionnaire	Adverse Events Questionnaire	Treatment Impact Questionnaire
Enrollment Visit	X	X	X	X	X	X	X	X		
1-week Call										
9-week Visit			X masked	X masked	X		X	X	X	X
18-week Visit			X masked	X masked	X	X		X	X	X
19-week Call*										
27-week Visit†			X	X	X			X	X	
36-week Visit†			X	X	X			X	X	

*19-week phone call timed 7 to 13 days after the 18-week primary outcome only for participants assigned to optical correction alone (if needed) who have residual amblyopia and accept randomization to treatment with Luminopia or Vivid Vision at the 18-week primary outcome.

†The 27-week and 36-week post-randomization visits are completed by any participant assigned to optical correction alone (if needed) who has residual amblyopia and accepts randomized allocation of treatment with either Luminopia or Vivid Vision at the 18-week primary outcome.

Chapter 1: Background Information

1.1 Epidemiology and Clinical Characteristics

Amblyopia is the most common cause of reduced monocular visual acuity (VA) in children and young adults, with estimates of prevalence ranging from 1% to 5%.[1,2] The most commonly associated risk factors are uncorrected anisometropia, strabismus, or a combination of both. In addition to reduced VA, amblyopia may also be associated with dysfunctions of accommodation, fixation, binocularity, vergence, reading speed and fluency, and contrast sensitivity.[3-12]

1.2 Current Practice

1.2.1 Monocular Penalization

The current foundation of amblyopia treatment is optical correction (when there is uncorrected refractive error) followed (if needed) by part-time patching or atropine penalization of the fellow eye.[13-18] While this has long been the standard treatment approach, it is known to be less effective when treating older children,[19] the majority stabilizing with residual amblyopia.[20-22]

In older children, there are limited data showing added benefit from monocular penalization with patching and/or atropine versus continued optical correction alone. A PEDIG randomized trial of patching 2-6 hours/day plus daily atropine versus continued glasses alone in 8-12 year olds (n=404) found 53% of the participants treated with patching and atropine improved 10 or more letters by 24 weeks compared with 25% of those continuing with optical correction alone (a difference of 28%, 95% confidence interval (CI) for difference = 19% to 37%).[22]

One possible reason for failure of part-time patching treatment in older children is poor adherence with the prescribed treatment regimens.[23,24] Nevertheless, data from studies using occlusion dose monitors show that adherence with patching in older children is no different than adherence in younger children,[25] yet treatment effect appears to decline with age, especially after 7 years.[19,22,25] Such data suggest that part-time patching and atropine may simply be inadequate treatment approaches in some older children with amblyopia. In addition, some children and their parents report adverse effects from patching, including negative psychosocial effects, bullying and social stigma.[26-30]

The limited effectiveness of standard treatment approaches results in many 8- to 12-year-olds having residual amblyopia. This, in addition to the challenges of acceptability with patching, calls for consideration of alternative amblyopia treatments that are better suited to older children.

1.2.2 Dichoptic Treatments

Although the predominant approach for amblyopia treatment is monocular penalization, some have advocated an alternative dichoptic (binocular) treatment approach. Dichoptic treatments for amblyopia provide simultaneous but separate stimulation to each eye, incorporating elements of binocular engagement, but modifying the input to the sound eye by blur and/or reduced contrast sensitivity and/or reduced luminance. Dichoptic treatment strategies may also differentially modify central versus peripheral vision and may utilize other motor skills such as those requiring hand-eye coordination. The neuro-physiological basis for dichoptic treatment is supported by

evidence that binocular cortical mechanisms remain intact even in adults with strabismic amblyopia.[31]

Over the past 20 years, dichoptic treatments have evolved from office-based technologies[32-34] to those that can be conducted in the home. Home-based technologies have many advantages, including convenience and the reduced cost associated with less in-office care-provider time. Current home-based dichoptic treatments typically utilize either games, movies, or web-based content.

Both dichoptic games and dichoptic movies have been previously studied to some extent in older children and adults with amblyopia, but there are very few data on outcomes specifically in 8- to 12-year-olds. To provide optimal relevance for the present study proposal, the following summary of prior data is limited to previous studies conducted by PEDIG and other studies on technologies that are currently available for future study and that do not require patching as part of the treatment approach.

1.2.2.1 Dichoptic Games

PEDIG has previously evaluated two dichoptic iPad games as treatment for amblyopia in randomized clinical trials: the Tetris falling blocks game in ATS18[35,36] and the Dig Rush game in ATS20.[37] In ATS18, the Tetris falling blocks game was found *not* to be non-inferior to patching, with an adjusted treatment group difference at 16 weeks in 5- to <13-year-olds of 0.31 lines, favoring patching (upper limit of the 1-sided 95% CI, 0.53 lines).[27] Nevertheless, only 22% completed >75% of prescribed gameplay. In the ATS20 older cohort (7- to 12-year-olds),[37] there was no difference in letter scores at 8 weeks between those randomized to the dichoptic Dig Rush game and those randomized to continued spectacles alone (adjusted mean difference: -0.1, 98.3% CI: -2.4 to 2.1 letters); 56% completed >75% of prescribed gameplay.[37]

These previous data strongly suggest that poor adherence with these types of games, accompanied by inattention and short, sporadic treatment sessions likely contributed to failure to show a benefit of this modality of dichoptic treatment.

Vivid Vision is a dichoptic game technology currently certified in the Europe Union (CE approved 2017). Vivid Vision utilizes a virtual reality (VR) mobile headset to display child-appropriate, interactive games and activities. Treatment of amblyopia is achieved by balancing interocular blur and/or luminance to restore perceptual contributions from the amblyopic eye. Binocular viewing is required for game play. The games require recognition of binocular cues targeting suppression, stereoscopic vision, and vergence, each treated in turn at the threshold of the patient's ability. There are no prior Vivid Vision outcome data specifically in 8- to 12-year-olds, but all prior studies are summarized below.

Ziak et al[38] used the beta version of Vivid Vision in 17 adults (age 17 to 69 years) with anisometropic amblyopia. After eight 40-minute in-office sessions (2 per week), mean amblyopic-eye VA improved from 0.58 ± 0.35 to 0.43 ± 0.38 logMAR (mean change: 0.15, 95% CI: 0.07 to 0.22 logMAR); 47% achieved 20/40 or better after treatment versus 30% before treatment.

Ho et al[39] (*poster presentation only*) used Vivid Vision over 8, 30-minute treatment sessions (one per week), to treat residual amblyopia in 34 patients aged 3 to 69 years. Data displayed in a bar chart suggest estimated mean change was 0.17 logMAR (95% CI: 0.16 to 0.18) in participants aged <=11 years (N=18) and 0.15 logMAR (95% CI: 0.11 to 0.19) in participants aged >11 years (N=16).

Halička et al[40] studied Vivid Vision in a single arm prospective study including 84 adults (aged 18-54 years) and found an average improvement of 0.1 logMAR (no standard deviation or 95% CI reported) after 4 weeks (8 hours) of in-office treatment.

Meqdad et al[41] studied Vivid Vision and patching in a randomized trial including 86 subjects aged 12 (range 6 to 37) years, and found an average improvement of 0.89 lines (95% CI: 0.73 to 1.35 lines; P< 0.001) after 10 weeks (20 hours) of in-office therapy.

1.2.2.2 Dichoptic Movies/Shows

Luminopia is a dichoptic movie technology (often termed a digital therapeutic with software as the medical device) available for use in the USA since 2022 and has been approved by the FDA for the treatment of amblyopia in children 4 to 7 years of age.

Luminopia displays a large library of web-based video content through a virtual reality (VR) headset, utilizing computational algorithms to split the source video into 2 streams (one to each eye) and modify the input in real time. Contrast in the sound eye is reduced to 15% and a series of 6 different dichoptic masks overlay the video content, rotating every 30 seconds. Complementary dichoptic masks are superimposed on the images such that binocular viewing is required to fully appreciate the video content. There are some limited prior data in older children.

In a single-arm pilot study (n=90)[42] evaluating a younger cohort with amblyopia (4- to 12-year-olds; mean 6.7±2.0 years), Luminopia was prescribed 1 hour/day for 12 weeks. Overall (n=74 outcomes) mean amblyopic-eye BCVA improved from 0.50±0.15 to 0.35±0.21 logMAR (1.5 logMAR lines, 95% CI, 1.2-1.8 lines, P<0.0001) over 12 weeks.[42] For the 17 participants aged 8 to 12 years, amblyopic-eye VA improved an average of 0.14± 0.11 logMAR after 12 weeks of treatment (95% CI, 0.09 to 0.19 logMAR).[42]

1.3 Choice of Study Design and Control Group

In designing this study, the planning committee carefully considered the most important questions to answer in this older age group. Over several months of discussion, it became clear that the planning committee, executive committee and investigator group had strong interest in answering treatment effectiveness questions for both a dichoptic game technology (Vivid Vision) and a dichoptic movie technology (Luminopia). As a result, the planning committee moved forward with the current proposal to include two active treatment groups.

Both glasses alone and part-time patching were considered as candidates for a control group but given the paucity of any evidence for effectiveness of dichoptic treatments in older children, it was considered necessary to first answer the basic question of whether there is any treatment benefit for dichoptic treatments when compared with continued optical correction alone if needed.

Therefore, this study is a 3-arm randomized trial designed to answer two primary questions:

1) Is Luminopia superior to continued optical correction alone (if needed)? and
2) Is Vivid Vision superior to continued optical correction alone (if needed)?

If both Vivid Vision and Luminopia are superior to continued optical correction alone (if needed), a formal comparison between the two dichoptic treatments (Luminopia versus Vivid Vision) will be made. If either Vivid Vision or Luminopia are not superior to continued optical correction alone (if needed), the difference between active treatment groups will be considered exploratory only.

It is noted for the comparison of Luminopia versus Vivid Vision, the absence of a statistically significant difference cannot rule out the presence of a clinically meaningful difference between active treatment groups. The test is powered assuming a difference between treatments as small as 3.75 letters with a standard deviation of 7.0 letters.

1.4 Rationale for Present Study

Successful treatment continues to be an elusive goal in older children with amblyopia and the protracted clinical course presents an ongoing healthcare burden. Standard patching treatment appears to be less effective in older children, with an outcome of residual amblyopia for many. In addition, patching may be difficult for social reasons, making adherence more challenging to achieve. Given these concerns, alternative treatments for older children with amblyopia need to be seriously considered.

Although previous PEDIG studies in older children failed to show effectiveness of dichoptic treatment for amblyopia, there were notable challenges in maintaining engagement and achieving adherence. Technologies that utilize a more immersive and engaging environment are more likely to maintain interest and result in improved adherence and greater treatment benefit. Further study is needed to evaluate the effectiveness of engaging and immersive home-based dichoptic treatments for amblyopia, to determine whether they provide a viable treatment option for those who refuse or are noncompliant with patching and atropine and to treat residual amblyopia in those previously treated.

In addition to evaluating VA outcomes, we plan to assess treatment impact to provide valuable data on patient experience with each dichoptic technology. We also plan to assess functional vision and social and frustration / worry quality of life to evaluate everyday life treatment benefits.

1.5 Potential Risks and Benefits of Study Treatment

1.5.1 Known Potential Risks

1.5.1.1 Luminopia

In a previous randomized clinical trial evaluating Luminopia vs continued glasses alone in children aged 4 to 7 years[43], 10 (20%) of 51 patients experienced non-serious adverse events in the treatment group vs. 7 (13%) of 54 patients in the continued glasses group. In the Luminopia treatment group adverse events were new heterotropia in 3 (6%), worsening VA in the

amblyopic eye in 2 (4%), worsening VA in the fellow eye in 2 (4%), headache in 4 (8%), eyestrain in 1 (4%), with single cases each of dizziness, increase in frequency of night terrors, eye twitching, and facial redness.

In the continued glasses group adverse events were diplopia in 1 (2%), new heterotropia in 2 (4%), worsening heterotropia in 1 (2%), worsening VA in the amblyopic eye in 4 (7%), headache in 1 (2%) and pain from glasses in 1 (2%). No serious adverse events were reported. The most frequent non-serious adverse event potentially related to Luminopia was headache (8%).

In a preceding non-randomized study evaluating 90 participants aged 4 to 12 years, [40] the most common adverse events were headaches (n=6), eye strain (n=3), blurry vision (n=2), and worsening VA (n=2). One participant developed a new strabismus. All adverse events were graded as mild in severity.

The Luminopia headset may become warm during normal usage. If the surface touching the face feels hot, the participant should stop using immediately and wait for it to cool down before re-using.

1.5.1.2 Vivid Vision

Meqdad et al[41] assessed participants aged 6 to 37 years after each week of treatment with Vivid Vision for any sense of dizziness, vertigo, diplopia, new / increasing tropia or worsening of VA in the fellow eye. A single patient reported tolerable diplopia in the first couple of treatment sessions which resolved spontaneously in subsequent sessions.[41] According to the Vivid Vision user manual, participants may experience temporary symptoms of eye strain, which may include blurred vision, a tired sensation, dry, irritated, or watery eyes, and fatigue. In addition, participants who have suffered a head injury, vertigo, a vestibular / balance / headache disorder, or who are at risk for photosensitive seizures may have exacerbated symptoms. Parents will be advised that the headset should be removed immediately if the participant feels nausea, dizziness, or headaches.

1.5.2 Known Potential Benefits

The potential benefits of treatment are improved amblyopic eye VA and improved stereoacuity.

1.5.3 Risk Assessment

The expected adverse events from Luminopia are summarized in 1.5.1.2 and do not pose a greater risk than what a typical child would experience in their normal day-to-day activities (e.g., wearing glasses, wearing small adhesives like band aids, watching television, playing videogames, etc.).

The expected adverse events from Vivid Vision are summarized in 1.5.1.2 and do not pose a greater risk than what a typical child would experience in their normal day-to-day activities (e.g., wearing glasses, wearing small adhesives like band aids, watching television, playing videogames, etc.).

Since Luminopia and Vivid Vision do not pose a significant risk to participants, the Sponsor has determined that both Luminopia and Vivid Vision are nonsignificant risk devices.

The Sponsor has determined that the protocol's level of risk is consistent with 45 CFR 46.404 and 21 CFR 50.51, which indicates research not involving greater than minimal risk.

1.6 General Considerations

The study is being conducted in compliance with the policies described in the 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).

Luminopia has been approved by the FDA for treatment of amblyopia in children aged 4 to 7 years for up to 12 weeks. In this younger population, serious side effects were rare. Risks are not expected to be different in children aged 8 to 12 years, or for the extended use. The delivery of virtual media using Vivid Vision is by means of a similar headset and therefore no significant risks are expected using Vivid Vision either. As such, both investigational devices are considered by the sponsor to be non-significant risk devices and are considered to have an approved application for investigational device exemption (conditioned upon IRB agreement of device risk determination), whereby compliance with the abbreviated requirements of 21 CFR 812.2(b) will be maintained.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

The study plans to enroll a minimum of 252 participants. As the enrollment goal approaches, sites will be notified of the end date for recruitment. Study participants whose parents have signed an informed consent form (and child has signed assent form, if required) can be enrolled up until the end date, which means the recruitment goals might be exceeded; however, total recruitment will not exceed 265 participants.

Study participants will be recruited from approximately 70 clinical centers in North America. All eligible participants will be included without regard to sex, race, or ethnicity. There is no restriction on the number of participants to be enrolled or randomized by each site toward the overall recruitment goal.

2.1.1 Informed Consent and Authorization Procedures

A child is considered for the study after undergoing a routine eye examination as part of standard of care that identifies amblyopia appearing to meet the eligibility criteria. Children may also be referred to a study investigator from another eye-care or health-care provider. The study will be discussed with the child's parent(s) or legal 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 and assent must be obtained from a parent and child prior to performing any study-specific procedures that are not part of the child's routine care and/or collecting any data for the study.

If the participant and/or parent(s) are not fluent in written or spoken English, then the consent and/or assent forms must be translated into a language understandable by the participant/parent(s). Further, a qualified interpreter must be available for the consent process and for all subsequent study-related interactions.

A participant is considered enrolled when the informed consent and assent forms have been signed, as applicable.

2.2 New or Change in Spectacle Correction If Needed

New spectacles or a change in spectacles may be prescribed for participants who have not had a cycloplegic refraction within 7 months *OR* if their current spectacles do not meet spectacle tolerance criteria (2.3 #6) *OR* in cases where the investigator determines that updating the spectacles is necessary for best clinical care, IF they ALSO meet ALL the other inclusion criteria (2.3) while wearing their current refractive correction.

The prescribed spectacles must be based upon a cycloplegic refraction performed on the day of enrollment or within 7 months and must meet eligibility criteria in 2.3 #6. If new spectacles are prescribed and paid for by the study, the investigator should ensure that visual acuity is still expected to meet eligibility criteria in 2.3 #2. As needed, VA should be measured (using the investigator's preferred VA testing method) in the intended spectacle prescription if the child is not cyclopleged or in the full cycloplegic refractive error if the child is cyclopleged.

The participant will return for standard of care visits until they meet eligibility criteria (including stability criteria) below in 2.3 #6.

Any new contact lenses or change to contact lenses will NOT be paid for by the study.

2.3 Participant Inclusion Criteria

Individuals must meet all the following inclusion criteria to be eligible to participate in the study.

1. Age 8 to <13 years.
2. VA, measured in each eye without cycloplegia in current refractive correction (if applicable) using the E-ETDRS VA protocol on a study-approved device displaying single surrounded optotypes, as follows:
    a. VA in the amblyopic eye 20/40 to 20/200 inclusive (33 to 72 letters with E-ETDRS).
    b. VA in the fellow eye 20/25 or better (≥ 78 letters with E-ETDRS).
    c. Interocular difference ≥ 3 logMAR lines (≥ 15 letters) i.e., amblyopic eye VA at least 3 logMAR lines worse than fellow eye VA).
3. Amblyopia associated with strabismus, anisometropia, or both (previously treated or untreated).
    a. Criteria for strabismic amblyopia: At least one of the following must be met:
        - Presence of a heterotropia on examination at distance or near fixation (with optical correction), must be <=5 prism diopters (Δ) by SPCT at distance and near fixation.
        - Documented history of strabismus which is no longer present (which in the judgment of the investigator could have caused amblyopia).
    b. Criteria for anisometropia: At least one of the following criteria must be met:
        - ≥1.00 D difference between eyes in spherical equivalent (SE).
        - ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes.
    c. Criteria for combined-mechanism: Both of the following criteria must be met:
        - A criterion for strabismus is met (see above).
        - ≥1.00 D difference between eyes in SE OR ≥1.50 D difference in astigmatism between corresponding meridians in the two eyes.
4. No more than 2 weeks (cumulative) of prior dichoptic treatment
5. No treatment with cycloplegic eyedrops (e.g., atropine) in the past 2 weeks; other treatments allowed up to enrollment but then must be discontinued.
6. Refractive correction is required (single vision lenses or contact lenses) for any of the following refractive errors based on a cycloplegic refraction completed within the last 7 months:
    - Hypermetropia of 2.50 D or more by SE
    - Myopia of amblyopic eye of 0.50D or more SE
    - Astigmatism of 1.00D or more
    - Anisometropia of more than 0.50D SE

NOTE: Children with cycloplegic refractive errors that do not fall within the requirements above for refractive correction may be given refractive correction at investigator discretion but must follow the study-specified prescribing guidelines, as detailed below.

NOTE: Monocular or binocular contact lens wear is allowed provided the contact lenses meet the refractive error correction requirements below. For each child, all testing must be performed using the same form of optical correction (i.e., no changing between contacts and spectacles).

a. Spectacles/contact lens correction prescribing instructions referenced to the cycloplegic refraction completed within the last 7 months:
   - SE must be within 0.50D of fully correcting the anisometropia (if new glasses are prescribed, reduction in plus sphere must be symmetric in the two eyes).
   - SE must not be under corrected by more than 1.50D SE.
   - Cylinder power in both eyes must be within 0.50D of fully correcting the astigmatism.
   - Axis must be within +/- 10 degrees if cylinder power is ≤1.00D, and within +/- 5 degrees if cylinder power is >1.00D.
   - Myopia must not be under corrected by more than 0.25D or over corrected by more than 0.50D SE, and any change must be symmetrical in the two eyes.

b. Spectacles/contact lens correction (with or without other treatment such as patching) meeting the above criteria must be worn:
   - For at least 18 weeks ***OR*** until VA stability is documented (defined as <1-line change by the same testing method measured on 2 consecutive exams at least 9 weeks apart).
     - For determining VA stability (non-improvement):
       - The **first** of two measurements may be made 1) in current correction, or 2) in trial frames with or without cycloplegia or 3) without correction (if new correction is prescribed),
       - The **second** measurement must be made without cycloplegia in the correct spectacles/contact lens correction that has been worn for at least 9 weeks.
       - *NOTE: Because this determination is a pre-randomization, the method of measuring VA is not mandated.*

7. Participant is willing to wear a headset.
8. Participant is willing to continue full-time spectacles/contact lens wear (if needed).
9. Interpupillary distance of 52mm to 72mm inclusive.
10. Investigator is willing to prescribe continued spectacles/contact lens correction (if needed) or either dichoptic device per protocol.
11. Participant is willing to accept assignment to either continued spectacles/ contact lens wear alone, dichoptic movies/shows (view 1 hour per day 6 days per week) OR dichoptic games (play approximately 25 minutes per day, 6 days per week) for 19 weeks.
12. Parent understands the protocol and is willing to accept randomization.
13. Parent has phone (or access to phone) and is willing to be contacted by JAEB Center staff.
14. Relocation outside of area of an active PEDIG site for this study within the next 36 weeks is not anticipated.

2.4 Participant Exclusion Criteria

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

1. Heterotropia more than 5Δ at distance or near (measured by SPCT in current correction)
2. Prism lenses or need of a prism prescription at enrollment.
3. Current bifocal spectacles (eligible only if bifocal discontinued 2 weeks prior to enrollment).
4. Myopia greater than -6.00D spherical equivalent in either eye.
5. Ocular co-morbidity that may reduce VA determined by an ocular examination performed within the past 7 months (*Note: nystagmus per se does not exclude the participant if the above visual acuity criteria are met using patch occlusion. Fogging is not permitted*).
6. Diplopia more than once per week over the last week prior to enrollment by parental report.
7. History of light-induced seizures.
8. Known simulator sickness.
9. Severe developmental delay that would interfere with treatment or evaluation (in the opinion of the investigator). Participants with mild speech delay or reading and/or learning disabilities are not excluded.
10. Immediate family member (biological or legal guardian, child, sibling, parent) of investigative site personnel directly affiliated with this study or an employee of the JAEB center for Health Research.

2.5 Procedures at Enrollment Visit

2.5.1 Historical Information

After informed consent has been signed, historical information elicited will include the following: date of birth, sex, race, ethnicity, current medication use, history of and current medical conditions, and prior amblyopia therapy including refractive correction.

2.5.2 Ability to Use Luminopia or Vivid Vision

Interpupillary distance will be measured using investigator's standard method or a PEDIG-provided IPD ruler. Participants with interpupillary distance <52mm or >72mm will not be eligible to participate in the study.

Site personnel will confirm that the participant is able and willing to wear the Luminopia or Vivid Vision headsets by:

1. Showing the child the devices in the clinic and allowing them to try them on, if desired.
2. Asking the child if they are willing to wear the headset for up to an hour a day, 6 days a week.

2.5.3 Clinical Testing

Participants who meet all eligibility criteria in section 2.3 and 2.4 including visual acuity stability criteria in current spectacles/contract lens correction will complete the following tests and assessments.

All examination procedures must be tested on the date of enrollment, except the cycloplegic refraction and ocular examination, which must be performed within 7 months prior to the day of enrollment. The following procedures should be performed at the enrollment visit in the following order:

Lensometry:
Verify current refractive correction by lensometry. If a participant is wearing contact lenses, verify contact lens prescription.

Questionnaires:

1. Assessment of Binocular Diplopia:
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may assess diplopia. Children who have reported diplopia more than once over the past week are ineligible (see section 2.3).
2. PedEyeQ Functional Vision Domain[44]:
   A child questionnaire for children, a proxy questionnaire completed by the parent regarding their child's functional vision. The child questionnaire is either completed by the child themselves or administered to the child by study personnel and the Proxy questionnaire is completed by the parent.
3. PedEyeQ Social Domain and Frustration/Worry Domain[44]:
   Child questionnaire for children, proxy questionnaire completed by the parent regarding their child. The child questionnaire is either completed by the child themselves or administered to the child by study personnel and the Proxy questionnaire is completed by the parent.

Clinical Testing (in the following order) **is performed in the participant's current refractive correction, if required, without cycloplegia:**

4. Distance Visual Acuity Testing:
   Monocular distance VA testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic E-ETDRS VA on a study-certified VA tester displaying single surrounded optotypes.
5. Binocular Function Testing (by a certified examiner):
   - Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
   - If nil stereoacuity on the Randot Preschool Test, the Random Dot Butterfly test will be performed at 40cms.

- If nil stereoacuity on the Random Dot Butterfly, the Worth 4-shape will be administered.

6. Ocular Alignment Testing:
   Ocular alignment will be assessed in current spectacle/contact lens correction by the cover test, simultaneous prism and cover test (SPCT) (in cases of strabismus detected by cover test), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter).
7. Additional Clinical Testing:
   Ocular examination as per investigator's clinical routine.

2.6 Randomization

The JAEB Center will construct a Master Randomization List using a permutated block design stratified by VA in the amblyopic eye as moderate (20/40 to 20/80 [72 to 53 letters]) versus severe (20/100 to 20/200 [52 to 33 letters]) which will specify the order of treatment group assignments.

All eligible participants enrolled in the study will be followed for up to 36 weeks. Participants will be randomly assigned in a 1:1:1 allocation to one of the following three treatment groups for 18 weeks:

- **Luminopia Group**: dichoptic movies/shows wearing the Luminopia headset prescribed 1 hour per day (treatment time can be split into shorter sessions totaling 1 hour each day) 6 days a week with current optical correction, if needed.
- **Vivid Vision Group**: dichoptic games using the Vivid Vision headset, prescribed approximately 25 minutes per day (treatment time to complete the day's sessions can be split into shorter sessions totaling about 25 minutes each day) 6 days per week with current optical correction, if needed.
- **Continued Optical Correction Group**: continued full-time optical correction alone, if needed.

Once a child is assigned to treatment, they will be included in the analysis regardless of whether the assigned treatment is performed. Thus, the investigator must not randomize a participant unless convinced that the parent will accept any of the treatments.

Chapter 3: Randomized Trial Procedures

3.1 Treatment

Investigators must not start any additional treatment (other than assigned treatment as outlined below) prior to the 18-week primary outcome visit.

3.1.1 Luminopia Dichoptic Group

Participants randomized to the Luminopia group will be asked to watch dichoptic movies/shows using the Luminopia device at home, for 1 hour per day, 6 days per week, for 18 weeks, while continuing to wear any optical correction (including while wearing the Luminopia device).

Parents will be instructed that the 1 hour of daily treatment should be completed in a single 60-minute session, but if this is not possible for whatever reason, the treatment may be divided into shorter sessions totaling 1 hour per day. Adherence with Luminopia treatment will be recorded electronically throughout the study and will be accessible by the study coordinator and investigator through the Luminopia online portal.

3.1.2 Vivid Vision Dichoptic Group

Participants randomized to the Vivid Vision group will be instructed to play dichoptic games using the Vivid Vision device with the Smart Assist 2 treatment program at home for approximately 25 minutes per day, 6 days per week, for 18 weeks while continuing to wear any optical correction (including while wearing the Vivid Vision device).

The therapy session can be paused by taking a rest with the headset on, or by taking the headset off. In either case, game play resumes when the headset is put back on. An unfinished session can be resumed at any time later on the same day, but sessions that are not completed within 10 hours of the start time will end. Any data will be saved. The next day, the next session will start, even if the previous session was not completed. Thus, participants will be instructed to complete one treatment session each day. Adherence with Vivid Vision treatment will be recorded electronically throughout the study and will be accessible by the study coordinator, investigator and by the parent through the Vivid Vision online portal.

3.1.3 Continued Optical Correction Group

Participants assigned to the continued optical correction group will continue to wear any needed refractive correction full-time for 18 weeks.

3.2 Phone Call

Site personnel will call all participants 1 week (7 to 13 days) after randomization to encourage adherence and confirm that there are no problems with randomized treatment. Site personnel will also call participants in the optical correction alone group who switch to Luminopia or Vivid Vision treatment at the 18-week primary outcome visit (7 to 13 days after the 18-week visit), again to encourage adherence with treatment and to confirm that there are no problems with the Luminopia or Vivid Vision device.

3.3 Follow-up Schedule Through 18-Week Primary Outcome

The follow-up schedule through 18-week primary outcome is timed from randomization:

Visit	Target Day Post-Randomization	Target Window Post-Randomization*	Allowable Window Post-Randomization
1-Week Phone Call	7 days	7 to 13 days	7 to 27 days
9-Week Office Visit	63 days	49 days to 77 days	42 days to 104 days
18-Week Primary Outcome	126 days	112 days to 140 days	105 days to 168 days

* Target window for phone calls is 7 to 13 days from previous office visit. Target window for office visits is target day +/- 2 weeks.

3.4 Continued Follow-up Post 18-Week Primary Outcome

Children originally randomized to Luminopia or Vivid Vision will end the study at 18 weeks.

Children originally randomized to continued optical correction alone whose amblyopia HAS NOT resolved (1 or more logMAR lines IOD is present with the originally amblyopic eye worse than fellow eye) at the 18-week primary outcome visit, will be offered randomization to an 18-week trial of dichoptic treatment (Luminopia or Vivid Vision); and if they accept treatment, will continue in follow-up as defined below. Otherwise, the study will end.

Visit	Target Day Post-18-week	Target Window Post-18-week*	Allowable Window Post-18-week
19-Week Phone Call	7 days	7 to 13 days	7 to 27 days
27-Week Office Visit	63 days	49 days to 77 days	42 days to 104 days
36-Week Office Visit	126 days	112 days to 140 days	105 days to 168 days

* Target window for phone call is 7 to 13 days from previous office visit. Target window for office visits is target day +/- 2 weeks.

3.4.1 Treatment Post 18-Week Primary Outcome

Participants will continue dichoptic treatment until the 36-week visit. No other treatment should be prescribed before the 36-week outcome visit.

3.5 Follow-up Visit Testing Procedures

Participants will be seen at follow-up visits as outlined in sections 3.3 and 3.4.

All procedures will be performed with the participant's current refractive correction without cycloplegia.

- If a participant currently wears spectacles or contact lenses but they are not available or are not within tolerance at the 9-week follow-up examination, testing may be performed with current correction in trial frames.
- Habitual refractive correction (meeting study requirements) must be worn for the primary outcome visit at 18 weeks.

A Masked Examiner must complete distance VA and binocular function testing at the 9, and 18-week visits. The masked examiner must be PEDIG certified for the required testing. All other assessments are unmasked. Prior to the Masked Examiner entering the room, participants and parents should be instructed not to discuss their treatment with the Masked Examiner.

The following procedures should be performed at each visit in the following order:

Lensometry (unmasked):
Verify current refractive correction by lensometry. If participant wearing contact lenses, verify contact lens prescription.

Questionnaires (all unmasked):

1. Assessment of Binocular Diplopia (at 9, and 18 weeks; and at 27, and 36 weeks if treated with Luminopia or Vivid Vision):
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may assess diplopia.
2. Adverse Events (at 9, and 18 weeks [all participants]; and at 27, and 36 weeks if treated with Luminopia or Vivid Vision):
   A standardized questionnaire will be administered to the parent to collect data on possible adverse events.
3. Treatment Impact Questionnaire (at 9, and 18 weeks):
   An item bank of participant-derived questionnaire items will be completed by the child themselves and by the child's parent (proxy rating regarding impact on their child and also questions regarding impact on the parent themselves). Questions pertain to the impact of the child's specific treatment on the child themselves and on the parent / family.
4. PedEyeQ Social Domain and Frustration/Worry Domain (at 9 weeks only):
   Child questionnaire for children and proxy questionnaire for the parent regarding their child. The Child questionnaire is either completed by the child themselves or administered to the child by study personnel and the Proxy questionnaire is completed by the parent.
5. PedEyeQ Functional Vision Domain (at 18 weeks only):
   A child questionnaire for children and proxy questionnaire for the parent regarding their child's functional vision. The child questionnaire is either completed by the child themselves or administered to the child by study personnel. The Proxy questionnaire is completed by the parent.

   Clinical Testing performed in the participant's current refractive correction (if required) without cycloplegia in the following order at ALL VISITS. Masked testing must be performed by a PEDIG certified examiner.
   - *Habitual refractive correction (meeting study criteria) is required for the 18-week primary outcome exam.*
   - *Testing in trial frames with current Rx is allowed at 9, 27 and 36 weeks if current refractive correction is not available or does not meet study criteria.*

6. Distance VA Testing (**at 9, and 18 weeks Masked**; at 27, and 36 weeks if applicable unmasked): Monocular distance VA testing will be performed in current refractive correction (if required) in each eye by a certified examiner using the electronic ATS-ETDRS on a study-certified VA tester displaying single surrounded optotypes.

7. Binocular Function Testing by a certified examiner in current refractive correction if required (**at 9, and 18 weeks masked**; at 27, and 36 weeks if applicable unmasked):
    a. Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
    b. If nil stereoacuity on the Randot Preschool Test, the Random Dot Butterfly test will be administered at 40cms.
    c. If nil stereoacuity on the Random Dot Butterfly, then the Worth 4-shape will be administered at 40cms.
8. Ocular Alignment Testing (Unmasked): Ocular alignment will be assessed by a certified examiner in current refractive correction (if required) by the cover test, SPCT (in cases of strabismus detected by cover test), and PACT in primary gaze at distance (3 meters) and at near (1/3 meter).
9. Adherence Monitoring (Unmasked): Adherence data for Luminopia and Vivid Vision will be downloaded and reviewed.

3.6 Masked Examiner

The Masked Examiner must be certified to test VA and binocular function testing. Because the Masked Examiner must be masked to the participant's treatment group they must be someone other than the managing clinician (in many cases the managing clinician will be the investigator, but this is not required).

3.7 Non-Study Visits and Treatment

Investigators may schedule additional visits at their own discretion. Participants will continue to follow the study-specified follow-up schedule regardless of any non-study visits. No data will be collected at non-study visits for the purpose of the study.

Investigators must not start any additional non-randomized treatment or stop randomized treatment prior to the 18-week primary outcome visit without first contacting a protocol chair.

For participants who continue in the study after 18 weeks, Luminopia or Vivid Vision treatment should continue until the 36-week visit with no other treatment prescribed prior to the 36-week outcome visit.

3.8 Management of Refractive Error

No cycloplegic refraction is mandated during the study. Nevertheless, if the investigator suspects that refractive error may not be corrected according to study guidelines, a cycloplegic refraction should be performed. If the new cycloplegic refraction compared to the old cycloplegic refraction differs by $\geq$0.75 D sphere or $\geq$0.75 D cylinder or $\geq$0.75 D in SE anisometropia or axis change of 6 degrees or more when cylinder is 1.00 D or more; then a change in spectacles is required. Whether to update the spectacles for smaller changes in refraction is at investigator discretion.

When new spectacles are prescribed, the refractive correction prescribed must meet the requirements as described in section 2.2 #6. The updated spectacles will be paid for by the study.

3.9 Management of Strabismus

Because of the short duration of the primary outcome for the study and the age group being studied, strabismus surgery is not allowed prior to the 18-week primary outcome visit.

If surgery must be performed, a protocol chair should be contacted and a masked exam prior to surgery scheduled. The participant should remain in the study and complete all necessary visits. If surgery is performed, it must be recorded in the comment section of the Follow-up Examination Form.

Chapter 4: Study Devices

4.1 Description of the Luminopia Device

Luminopia is a software-only digital therapeutic designed to be used with commercially available Head-Mounted Displays (HMDs) which are compatible with the software application. The software application requires an internet connection for treatment. The Luminopia medical software application presents slightly different video content to each eye to encourage amblyopic eye usage. Treatment using Luminopia will be prescribed for 1 hour per day, 6 days per week.

4.1.1 Headset

The study will provide each participant with a VR headset pre-loaded with Luminopia software. The VR headset has a screen resolution of 564 pixels per inch, which constitutes the minimum display resolution requirement. The Luminopia system has been approved by the FDA for the treatment of moderate or severe amblyopia in children 4 to 7 years of age.

The Luminopia device should only be used in accordance with the manufacturer's instructions. The Luminopia device should only be used in a safe and stationary environment with the HMD connected to Wi-Fi. Luminopia should only be used with the participant seated or lying down. If the participant experiences discomfort because the Luminopia device feels too heavy, the participant should try to use the Luminopia device while lying down on their back.

The HMD should be kept away from heat sources, water, moisture, open flames, or direct sunlight. If the participant intends to use the Luminopia device away from home for an extended period of time, the parent should bring the charger provided with the HMD to charge the device as needed. The participant should not use the Luminopia device while the HMD is charging.

4.2 Description of Vivid Vision

Vivid Vision utilizes gamification to provide dichoptic anti-suppression therapy to treat amblyopia in an engaging VR game-based format. Each session is approx. 23 to 27 minutes and includes 3 to 4 games which vary each day to increase engagement with the therapy. The therapy is programmed such that the "visual" difficulty is separate from the "game" difficulty; the program continually adjusts to keep both visual and game difficulty at an appropriate level for the child. As vision improves, the size of the amblyopic eye target decreases, fellow eye blur decreases, and fellow eye contrast increases, binocular disparity decreases, and vergence demand increases.

Vivid Vision includes four games that focus on anti-suppression (Hoopie, Ring Runner, Breaker, Pepper Picker). Each game has multiple levels to keep the participant engaged. Vivid Vision therapy also includes disparity tuning guided therapy (popping bubbles game and bullseye target shooting game) to enhance binocularity. For children who have approx. 600 arc sec of contour-based lateral stereoacuity or better, games also include orthoptic vergence therapy to improve binocularity. Anti-suppression therapy continues throughout the therapy program.

4.2.1 Headset

The prescribed software will run on a stand-alone/all-in-one headset (DPVR P1 Pro). The headset has an on/off button, volume control, and USB port for charging. It is secured to the head by an adjustable head strap. The DPVR P1 Pro headset is a three-degrees-of-freedom (3DoF) headset, designed to be used by the participant-user in a comfortable seated position. It should not be used while standing or walking.

The Vivid Vision device should only be used in a safe and stationary environment. Vivid Vision should only be used while the participant is seated. If the participant experiences discomfort because the device feels too heavy, the participant should try to use the Vivid Vision device while leaning their head back on a high-backed chair.

The HMD should be kept away from heat sources, water, moisture, open flames, or direct sunlight. If the participant intends to use the device away from home for an extended period of time, the parent should bring the charger provided with the HMD to charge the device as needed.

4.2.2 Vivid Vision Handheld Controller

A handheld remote-control device called the hand controller is used to interact with the games during game play. The hand controller communicates with the headset via wireless bluetooth and is “paired” with a particular headset. It detects changes of orientation in space (3DoF), but not changes in position. It communicates with the Headset wirelessly to transmit information about the orientation and button presses of the remote controller.

4.2.3 Vivid Vision Patient Portal

Two levels of access to the participant's data are provided during treatment: the Site Portal and the Patient Portal. The Site Portal allows a study site to monitor adherence, session times, missed sessions, and treatment progress for each patient at that site. Notifications are sent to the Site Portal in case of red flag events such as missed treatment sessions or unexpected loss of performance. The Patient Portal allows the parent to monitor their child's adherence and session times, using a secure login.

4.3 Internet Requirements

Potential study participants who do not have the required internet capabilities in their home will be provided Wi-Fi access using a Hotspot at no cost for the duration of the study.

4.3.1 Luminopia

Wireless internet with Wi-Fi speed near the router that exceeds 5 Mbs is required to operate Luminopia. Faster network speeds will result in a better product experience.

4.3.2 Vivid Vision

Prior to the first session at home, a Wi-Fi connection should be made in order to connect the headset to the internet. The Wi-Fi connection can be made using either a home Wi-Fi network or a mobile hotspot device. If the headset loses connectivity afterward, then the session will still proceed, with visual difficulty being updated according to the previous session. When the headset reconnects, a local copy of the data will be uploaded to the server. The best practice is to remain connected to the internet so that data will be transferred immediately. A daily connection

would be acceptable. After one week of not connecting, the session may not be able to continue until connecting again.

4.4 Device Delivery and Return

Device Delivery and Return procedures will be detailed in the site instruction manual.

4.5 Device Accountability Procedures

Device accountability procedures will be detailed in the site instruction manual.

4.5.1 Device Failure

Parents will be provided with written instructions regarding the process to follow should the Luminopia or Vivid Vision device fail. If the device needs to be replaced PEDIG will provision a replacement.

4.5.2 Participant Access to Study Device After 18-Week Primary Outcome

Participants randomly assigned to receive continued optical correction alone who have not resolved at the 18-week primary outcome visit, will be offered random allocation to a trial of Luminopia or Vivid Vision therapy and if accepted, followed forward with a 19-week phone call and follow-up visits at 27-weeks and 36-weeks post-randomization. Luminopia or Vivid Vision therapy will NOT continue beyond the 36-week visit.

Participants randomly assigned to receive Luminopia or Vivid Vision will end treatment after the 18-week primary outcome visit.

Chapter 5: Testing Procedures and Questionnaires

5.1 Questionnaires

1. Assessment of Binocular Diplopia:
   An estimate of the frequency of diplopia (if any) will be determined by asking the parent "has your child complained of double vision over the last week." If yes, the parent is asked how frequently during the last week the child has complained of double vision: "once per week," or "2 to 3 times per week," or "4 or more times per week." Any study personnel may ask the parent to rate diplopia. Testing time is approximately 1 minute.

2. PedEyeQ Functional Vision Domain:
   A child questionnaire for children and a proxy questionnaire completed by the parent regarding their child's functional vision. The child questionnaire is either completed by the child themselves or administered by study personnel and the Proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

3. PedEyeQ Social Domain:
   A child questionnaire for children and a proxy questionnaire completed by the parent regarding their child's Social concerns. The child questionnaire is either completed by the child themselves or administered by study personnel and the Proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

4. PedEyeQ Frustration / Worry Domain:
   A child questionnaire for children, a proxy questionnaire completed by the parent regarding their child's Frustration / Worry. The child questionnaire is either completed by the child themselves or administered by study personnel and the Proxy questionnaire is completed by the parent. The questionnaires take about 3-4 minutes to complete.

5. Treatment Impact Questionnaire:
   An item bank of participant-derived questionnaire items will be completed by the child themselves and by the child's parent (proxy rating regarding impact on their child and also questions regarding impact on the parent themselves). Questions pertain to the impact of the child's specific treatment on the child themselves and on the parent / family. Testing is anticipated to take 5-7 minutes.

6. Adverse Event Questionnaire:
   A standardized questionnaire will be administered to the parent to collect data on possible adverse events. The questionnaire is anticipated to take 1 minute to complete.

5.2 Clinical Assessments

The following procedures will be performed at each visit as defined in the *ATS Procedures Manual:*

7. Distance VA Testing:
   Monocular distance VA testing will be performed in refractive correction if required in each eye by a certified examiner using the electronic ETDRS VA protocol on a study-certified VA tester displaying single surrounded optotypes.
   The VA protocol used at enrollment will be used throughout the study regardless of age at follow-up. Testing time for both eyes typically is in the range of 5 to 15 minutes.

8. Binocular Function Testing (by a certified examiner):
   Stereoacuity will be tested at 40cms in current refractive correction using the Randot Preschool Test.
   - If nil stereoacuity on the Randot Preschool Test, then the Random Dot Butterfly test will be administered at 40cms.
   - If nil stereoacuity on the Random Dot Butterfly, the hand-held Worth 4-Shape test will be performed at 40 cm.
   - Testing typically takes 3-5 minutes.

9. Ocular Alignment Testing: Ocular alignment will be assessed by a certified examiner in current refractive correction if required by the cover test, simultaneous prism and cover test (SPCT) (in cases of strabismus detected by cover test), and prism and alternate cover test (PACT) in primary gaze at distance (3 meters) and at near (1/3 meter). Testing time is typically 1 to 3 minutes.

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 Treatment

Any new or changes to optical correction will be paid for during the study.

For those randomized to Luminopia or Vivid Vision, the cost of prescribed dichoptic treatment for 18-weeks will be paid for by the study.

For those randomized to continued optical correction (if needed) who have residual amblyopia at 18 weeks, the cost of dichoptic treatment with Luminopia or Vivid Vision through 36-weeks will be paid for by the study.

For those randomized to Luminopia or Vivid Vision, the study will not pay for continued Luminopia or Vivid Vision game treatment outside the study.

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: Unanticipated Problem / Adverse Event Reporting

7.1 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 participant 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.

7.2 Adverse Events

7.2.1 Reportable Adverse Events

Because study treatments with Luminopia and Vivid Vision are non-invasive and consistent with usual clinical care, it is not expected that there would be significant adverse events other than those already being captured as part of the clinical outcome assessments or questionnaire (e.g., worsening of fellow eye VA, development of new or worsening strabismus, new diplopia, or report of headache, eyestrain, nausea, seizures, dizziness, increase in frequency of night terrors, or skin irritation).

7.2.2 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.

7.2.3 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 (see section 7).

7.2.4 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 18-week Primary Outcome Visit with permission from the parent to allow ongoing data collection.

Chapter 8: Statistical Considerations

8.1 Statistical and Analytical Plans

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

8.2 Study Objective and Statistical Hypothesis

8.2.1 Primary Efficacy Outcomes

The primary efficacy outcome will be the change in amblyopic eye distance VA (measured in letters) from randomization to 18 weeks. Change in letters will be calculated as [outcome VA] – [randomization VA] such that a positive change indicates improvement in VA letter scores, and a negative change indicates worsening.

8.2.2 Study Objectives

The primary objectives of the study in children 8 to 12 years of age are:

1. To formally compare the effectiveness of Luminopia 1 hr / day 6 days per week while wearing optical correction if needed (hereafter LUMINOPIA) versus continued optical correction alone if needed (hereafter GLASSES), in children 8 to 12 years of age, as a superiority study; and
2. To formally compare the effectiveness of Vivid Vision 25 minutes / day 6 days per week while wearing optical correction if needed (hereafter VIVID VISION) versus GLASSES, in children 8 to 12 years of age, as a superiority study.

If mean 18-week VA with LUMINOPIA and VIVID VISION are <u>both</u> significantly different from GLASSES, then a hypothesis test will:

1. Formally compare the effectiveness of LUMINOPIA vs VIVID VISION after 18 weeks of treatment as a superiority study.

If the mean 18-week change in VA with LUMINOPIA and/or VIVID VISION is not significantly different than GLASSES, then the difference between active treatment groups will be considered exploratory only.

8.2.3 Hypotheses

The study is designed to test two, two-sided superiority hypotheses, each designed to evaluate whether the mean change in VA from baseline at 18 weeks with GLASSES is significantly different than either dichoptic treatment (with LUMINOPIA or with VIVID VISION):

Superiority Test 1:	Superiority Test 2:
H_0: $\mu_{LUMINOPIA}-\mu_{GLASSES} = 0$ letters	H_0: $\mu_{VIVID\ VISION}-\mu_{GLASSES} = 0$ letters
H_a: $\mu_{LUMINOPIA}-\mu_{GLASSES} \neq 0$ letters	H_a: $\mu_{VIVID\ VISION}-\mu_{GLASSES} \neq 0$ letters

For each hypothesis, the difference in mean VA change at 18 weeks between treatment groups (LUMINOPIA minus GLASSES and VIVID VISION minus GLASSES), and a two-sided 95% confidence interval (CI) for the difference will be constructed.

Each hypothesis will be tested independently, such that each will be conducted with an alpha level of 0.05. Although two pairwise comparisons are being evaluated, there will be no formal adjustment to the familywise error rate; because the main objective of this trial is to compare two dichoptic treatments with different mechanisms of action with a shared control group, and not one another, an adjustment (e.g., Bonferroni) is not needed.[45-47] The risk of a false positive finding with this approach is lower than if each hypothesis were evaluated in two separate studies with different control groups.

If mean 18-week change in VA with LUMINOPIA and VIVID VISION are both superior to GLASSES, then a hypothesis test will evaluate whether there is a difference between active treatments with no adjustment to alpha (per the fixed sequence method):

Superiority Test 3:

H_0: $\mu_{\text{LUMINOPIA}} - \mu_{\text{VIVID VISION}} = 0$ letters

H_a: $\mu_{\text{LUMINOPIA}} - \mu_{\text{VIVID VISION}} \neq 0$ letters

The difference between treatment groups (LUMINOPIA minus VIVID VISION), and a two-sided 95% CI for the difference will be constructed, with *p*-value.

However, if the mean 18-week change in VA with either LUMINOPIA or VIVID VISION is not significantly different than GLASSES, then the difference between active treatment groups will be considered exploratory and a *p*-value will not be reported.

8.3 Sample Size

8.3.1 Effect of GLASSES

To estimate the treatment effect for those randomized to GLASSES in the current study, VA data for participants prescribed continued optical correction alone in a previous PEDIG study, ATS20, were used.

The data were limited to participants who met the eligibility criteria for the current study. In ATS20, 114 participants between the ages of 8 and 12 experienced a 2.2 letter (95% CI 1.2 to 3.2) mean improvement in VA after 8 weeks of full-time optical correction alone, with a standard deviation of 5.1 letters (95% CI 4.6 to 5.9).

8.3.2 Effect of LUMINOPIA

Xiao et al conducted a single-arm pilot study (n=90)[48] in children with amblyopia aged 4 to 12 years (mean 6.7±2.0 years). Luminopia was prescribed 1 hour/day for 12 weeks. Overall (n=74 outcomes) mean amblyopic-eye BCVA improved from 0.50±0.15 to 0.35±0.21 logMAR (1.5 logMAR lines, 95% CI = 1.2-1.8 lines, $P<0.0001$) over 12 weeks.[48]

For the 17 participants aged 8 to 12 years, amblyopic-eye VA improved an average of 1.4±1.1 logMAR lines after 12 weeks of treatment, corresponding to a mean of 7 letters (95% CI, 4.2 to 9.8) and SD of 5.5 letters (95% CI, 4.1 to 8.4).[48]

8.3.3 Effect of VIVID VISION

Ziak et al[49] used the beta version of Vivid Vision in 17 adults (age 17 to 69 years) with anisometropic amblyopia. After eight 40-minute in-office sessions (2 per week), mean amblyopic-eye VA improved from 0.58 ± 0.35 to 0.43 ± 0.38 logMAR (mean change = 0.15 [95% CI: 0.07 to 0.22] logMAR; SD = 0.15 [95% CI: 0.11 to 0.22] logMAR). In letters, this corresponds to a mean change of 7.5 [95% CI: 3.5 to 11.0] letters; SD = 7.5 [95% CI: 5.5 to 11.0] letters by the 4-week outcome. The proportion with VA 20/40 or better increased from 30% to 47% after treatment.

8.3.4 Summary of Previous Studies

Data from previous studies are summarized in Table 1 below.

Table 1 – Summary of Previous Studies in Older Children

Study	Time on Treatment	N	Mean Change from Baseline (95% CI for Mean)	SD for Change from Baseline (95% CI for SD)
Continued Optical Correction Alone				
ATS20 RCT, 8-12 years, Glasses Alone with Heterotropia <=5 pd at near by SPCT	8 weeks	N=114	2.2 letters (1.2 to 3.2)	5.1 letters (4.6 to 5.9)
Luminopia				
Xiao et al. 2021 (non-RCT, age 8-12 years)	12 weeks	N=17	7 letters (4.2 to 9.8)	5.5 letters (4.1 to 8.4)
Vivid Vision				
Ziak et al. 2017 (non-RCT, age 17-69 years)	4 weeks	N=17	7.5 letters (3.5 to 11.0)	7.5 letters (5.5 to 11.0)

8.3.5 Sample Size for Superiority of Each Dichoptic Treatment Versus GLASSES

Table 2 displays the estimated sample sizes corresponding to various treatment group differences (3 to 5 letters) and standard deviations (6, 7, or 8 letters). A common standard deviation (SD) of 7.0 letters and a true mean difference of 3.75 letters favoring dichoptic treatment (either LUMINOPIA or VIVID VISION) versus GLASSES after 18 weeks were selected to calculate the required sample size.

With a two-sided Type 1 error rate of 0.05 for each comparison, the study would require 75 participants in each group to achieve 90% power to reject the null hypotheses that the mean changes in VA between each dichoptic treatment and GLASSES are not different in favor of an alternative hypothesis that they differ (Table 2). Therefore, a total of 225 participants would be necessary to conduct the trial with sufficient power for each of 2 comparisons (75 participants each for LUMINOPIA, VIVID VISION, and GLASSES) assuming no loss to follow-up.

Accounting for 10% loss to follow up in each treatment group (75/.90), the total sample size would increase to 252 (84 participants in each group).

Table 2. Total Sample Size Estimates* for Testing Superiority of Each Dichoptic Treatment vs. GLASSES

	Standard Deviation (Letters)					
	6		7		8	
TRUE Difference (Letters)	N per Group	N Total	N per Group	N Total	N per Group	N Total
3.00	86	258	116	348	151	453
3.25	73	219	99	297	129	387
3.50	63	189	86	258	111	333
3.75	55	165	**75**	**225**	97	291
4.00	49	147	66	198	86	258
4.25	43	129	58	174	76	228
4.50	39	117	52	156	68	204

*Cells reflect total sample size unadjusted for loss to follow up with two-sided alpha 0.05, and 90% power for each comparison.

8.3.6 Power and Precision for Superiority of LUMINOPIA vs. VIVID VISION

It is noted that the study is not specifically powered for this objective because evaluation of this hypothesis is conditional on both LUMINOPIA and VIVID VISION being shown to be superior to GLASSES. Power is based on the same mean difference and standard deviation assumptions as the primary hypotheses. Failure to reject the null hypothesis of no difference may not rule out the possibility of a clinically meaningful difference between LUMINOPIA and VIVID VISION.

Powers for rejecting a two-sided null hypothesis of no difference in favor of an alternative hypothesis that the treatment groups differ is given in Table 3 for various estimates of standard deviation (6, 7, and 8 letters) and various true treatment group differences (1, 2, 3, 4, and 5 letters) using a Type 1 error rate of 0.05 and 75 participants in each treatment group.

Table 3. Power for Testing Superiority of LUMINOPIA vs. VIVID VISION

	True Mean Difference				
	1 letter (0.02 logMAR)	2 letters (0.04 logMAR)	3 letters (0.06 logMAR)	4 letters (0.08 logMAR)	5 letters (0.10 logMAR)
SD	Power	Power	Power	Power	Power
6 letters	17%	52%	86%	98%	99%
7 letters	14%	41%	74%	93%	99%
8 letters	11%	33%	62%	86%	96%

* N=75 per treatment group, 2-sided alpha (Type 1 error rate) = 0.05

Table 4 summarizes the half-width of a 95% confidence interval for a treatment group difference between LUMINOPIA and VIVID VISION for various pooled standard deviations with a sample size of 75 in each treatment group.

Table 4. Half-width 95% Confidence Intervals of the Treatment Group Difference for LUMINOPIA vs. VIVID VISION at Various Standard Deviations

Sample Size	SD = 6 letters	SD = 7 letters	SD = 8 letters
N=75 LUMINOPIA N=75 VIVID VISION	± 1.94	± 2.26	± 2.58

* With a Type 1 error rate of 0.05, and 75 participants per treatment group, the numbers in the cells represent the estimated half-width 95% confidence interval at the given standard deviation (6, 7, or 8 letters).

8.4 Outcome Measures

8.4.1 Primary Efficacy Endpoint

- Change in amblyopic eye distance VA from baseline at 18 weeks.

8.4.2 Secondary Efficacy Endpoints

- Change in child and proxy PedEyeQ Functional Vision domain scores from baseline at 18 weeks.
- Change in child and proxy PedEyeQ Social domain scores from baseline at 9 weeks.
- Change in child and proxy PedEyeQ Frustration/Worry domain scores from baseline at 9 weeks.

8.4.3 Exploratory Efficacy Endpoints

- Change in amblyopic eye distance VA at 9 weeks.
- Change in amblyopic eye distance VA over 18 weeks (area under the curve).
- Improvement of amblyopic eye distance VA by 2 or more lines (≥ 10 letters) at 9 weeks and 18 weeks, respectively.
- Resolution of amblyopia at 9 and 18 weeks
- Change in binocular function score from baseline at 9 and 18 weeks.
- Child, proxy, and parent Treatment Impact Questionnaire scores at 9 weeks and 18 weeks.

8.5 Analysis Datasets and Sensitivity Analyses

Analyses will follow the intent-to-treat principle (ITT); all participants will be analyzed according to their randomized treatment group, irrespective of adherence or compliance. However, a per protocol analysis will be performed for the primary outcome to evaluate the sensitivity of the results to substantial deviations from the protocol (details to be outlined in the statistical analysis plan [SAP]). The intent-to-treat analysis is considered primary. If the results of the per-protocol analysis and intent-to-treat give inconsistent results, exploratory analyses will be performed to evaluate possible factors contributing to the differences.

8.6 Analysis of the Primary Efficacy Outcome

The primary outcome, change in amblyopic-eye distance VA letter score from baseline at 18 weeks, is a continuous outcome that will be analyzed using an analysis of covariance (ANCOVA) model to estimate the adjusted mean difference between GLASSES and LUMINOPIA, as well as between GLASSES and VIVID VISION. The model will adjust for baseline amblyopic-eye distance VA. The adjusted between-group mean differences and two-sided 95% CIs and *p*-values will be reported. If an imbalance of factors between treatment groups is observed, a sensitivity analysis may be performed to control for these potential confounders.

Superiority of the dichoptic treatment (either LUMINOPIA or VIVID VISION) compared to GLASSES will be declared if the two-sided 95% CI for the difference between treatment groups in mean change in distance VA letter score from baseline to 18 weeks excludes 0 letters.

If both dichoptic treatments are declared superior to GLASSES, then a test of superiority between LUMINOPIA and VIVID VISION will be performed without further adjustment for multiplicity (see Section 8.14). The same analysis approach will be used. If either of the dichoptic treatments are not declared superior to GLASSES, then LUMINOPIA and VIVID VISION will still be compared, however, the comparison will be considered exploratory, and a *p*-value will not be presented.

Participants who do not complete the 18-week visit will have their 18-week amblyopic eye distance VA imputed. Markov chain Monte Carlo multiple imputation with 100 imputations will be used to impute missing data; variables in the imputation model will include amblyopic-eye VA at baseline, 9, and 18 weeks. Imputation will be carried out separately for each treatment group.[50] Reasons for which a participant may not complete the 18-week visit are outlined in section 8.8, "Intercurrent Events."

The ANCOVA model assumptions of linearity, normality, and homoscedasticity will be verified with graphical methods. If assumptions are seriously violated, then an alternative approach such as transformation of dependent or independent variables, elimination or categorization of continuous covariates, a robust method, or a nonparametric method may be considered.

As a sensitivity analysis, the primary outcome will be analyzed using complete cases rather than the imputed data. If the results from these analyses are discordant, then differences between participants with and without complete visit data will be evaluated.

8.7 Analysis of the Secondary Efficacy Outcomes

Secondary analyses will test the null hypothesis of no difference between treatment groups. For any given secondary outcome, if both LUMINOPIA and VIVID VISION are superior to GLASSES, then LUMINOPIA and VIVID VISION will be compared without further adjustment to the type 1 error rate.[51] If, however, both dichoptic treatments are not superior to GLASSES, then a *p*-value for the comparison of LUMINOPIA vs VIVID VISION will not be presented. See section 8.14 for more information on how multiplicity will be handled.

8.7.1 Pediatric Eye Disease Questionnaire (PedEyeQ)

The effect of amblyopia on quality of life will be evaluated using the PedEyeQ questionnaire. Scores on Functional Vision, Frustration/Worry, and Social domains will be assessed for both child and proxy (parent answering on behalf of the child) at baseline as well as at the visit week indicated below (Table 5). The responses of child and proxy will be Rasch scored according to reference tables and standardized on a ratio scale ranging from 0 to 100.[44]

Table 5. Structure of the PedEyeQ Analysis: Domains and Respondents

	Domain			
Respondent Level	**Social (9 weeks)**	**Frustration/Worry (9 weeks)**	**Functional Vision (18 weeks)**	**Outcomes**
Child	1	1	1	3
Proxy	1	1	1	3
				Total = 6

Change in PedEyeQ scores are continuous variables that will be analyzed with analysis of covariance (ANCOVA) to assess the differences between treatment groups across all domains and respondents (3 domains × 2 respondents = 6 outcomes) as shown in Table 5.[52] Models will be adjusted for enrollment scores. The treatment effect will be summarized as a mean difference and 95% CI. Similar to the primary outcome, missing data will be imputed using multiple imputation with baseline and outcome scores included in the imputation model and stratified by treatment group.

8.8 Intervention Adherence

At 9, and 18 weeks, the investigator will assess participant adherence to the assigned treatment. For each participant randomized to LUMINOPIA or VIVID VISION, the number of dichoptic treatment hours will be categorized according to percentage of prescribed treatment time as 75-100%, 50-75%, or <50%. Calendar data for the GLASSES group will not be analyzed other than a subjective assessment by the investigator of adherence at 9, and 18 weeks as Excellent, Good, Fair, or Poor after review of the calendar and interview with the parent. The tabulation of data related to treatment adherence is intended for exploratory purposes only, and therefore formal comparisons between treatment groups will not be performed.

8.9 Protocol Adherence and Retention

Protocol deviations and visit completion rates (excluding participants who die before the end of the visit window) will be tabulated for each treatment group.

8.9.1 Intercurrent Events

If any of the following events take place before the 18-week outcome, missing follow-up data will be imputed for the participant experiencing the event in the primary ITT analysis.

- Death
- Lost to follow up
- Withdrawal

If any of the following events occur before the 18-week outcome, data will not be imputed for participants experiencing these events, since the event itself does not preclude completion of study visits. Thus, the observed data at the 18-week outcome visit will be utilized.

- Treatment discontinuation
- Treatment crossover
- Receipt of non-protocol treatment

8.10 Safety Analyses

The cumulative proportions of each of the following adverse events by treatment group will be assessed at the initial study phase (enrollment to 18 weeks) and during the post-primary phase for those originally randomized to GLASSES (18 weeks to 36 weeks). During the initial study phase, the proportions will be compared statistically between all three groups using Fisher's Exact Test; if the p-value is $\leq .05$, then pairwise tests will be performed without further adjustment for multiplicity. As type II error (false negative) is more of a concern than type I error (false positive) in safety analyses, we will use $p \leq 0.05$, without adjustment for multiplicity, to define statistical significance in all safety analyses. It is noted that the study is not specifically powered to detect differences in safety outcomes and that the absence of a significant difference should not be viewed as evidence for the absence of a true difference. The proportion of adverse events occurring during the post-primary phase for original glasses participants will be tabulated within each dichoptic treatment group (LUMINOPIA or VIVID VISION) without formal statistical comparison.

- Worsening of best-corrected fellow-eye distance VA of 2 lines (10 letters) or more
- New onset strabismus >5 Δ by SPCT in participants with no strabismus at baseline
- Strabismus >10 Δ by SPCT in participants with strabismus at baseline
- Parental report of diplopia occurring more than once per week
- Skin irritation
- Headache
- Eyestrain
- Dizziness
- Night terrors
- Eye twitching
- Facial redness

The PEDIG DSMC will review safety data tabulated by treatment group at each of its semi-annual meetings and can request formal statistical comparison of any safety outcome at any time if they have cause for concern.

8.11 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics will be tabulated by randomized treatment group, and summary statistics appropriate to their distributions will be reported.

8.12 Interim Analyses

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 analyses and/or guidelines for stopping the study for futility or efficacy are pre-specified (see section 7).

8.13 Subgroup Analyses

Subgroup analyses, i.e., assessments of effect modification, will be conducted for the primary outcome. These analyses will be considered exploratory. Missing data will be imputed like the primary analyses except that the subgroup factors of interest, specified below, will be included in the imputation model, which will be stratified by treatment group. Within-subgroup mean differences for the treatment effects with 95% CIs will be estimated for each subgroup by adding an interaction term to the primary analysis models. Results will be presented as forest plots; *p*-values will not be presented.

The baseline factors to be evaluated in pre-planned exploratory subgroup analyses include amblyopic-eye distance VA (categorized), type of amblyopia, prior treatment for amblyopia, age (8 to <10 years or 10 to <13 years), and binocularity. The SAP will provide specific details on categorizations. The subgroup analysis by amblyopic-eye distance VA is considered of greatest interest.

There are no data to suggest that the treatment effect will vary by sex, race, or ethnicity. However, each of these factors will be evaluated in exploratory subgroup analyses as mandated by National Institutes of Health (NIH) guidelines.

8.14 Multiple Comparisons / Multiplicity

For the primary outcome, two tests of superiority for 18-week mean change in amblyopic eye distance VA will be conducted: LUMINOPIA vs GLASSES and VIVID VISION vs GLASSES. The tests will be performed independently, such that each will be conducted with an alpha level of 0.05.

Although two pairwise comparisons are being evaluated, there will be no formal adjustment to the familywise error rate; because the main objective of this trial is to compare two dichoptic treatments with different mechanisms of action with a shared control group, and not one another, an adjustment (e.g., Bonferroni) is not needed.[45-47] The risk of a false positive finding with this approach is lower than if each hypothesis were evaluated in two separate studies with different control groups. The same logic applies to secondary, exploratory, safety, and subgroup analyses.

For the comparison of LUMINOPIA vs VIVID VISION, the familywise error rate will be controlled with a hierarchical (i.e., fixed sequence) approach. If the null hypotheses for LUMINOPIA versus GLASSES and VIVID VISION versus GLASSES are rejected, then LUMINOPIA and VIVID VISION will be compared without further adjustment to the type 1 error rate.[51] If, however, both null hypotheses are <u>not</u> rejected, then the comparison of LUMINOPIA vs VIVID VISION will be considered exploratory and a *p*-value will not be presented. It is noted for the comparison of LUMINOPIA versus VIVID VISION, the absence of a statistically significant difference cannot rule out the presence of a clinically meaningful difference between active treatment groups. The study is powered assuming a difference in VA between treatments as small as 3.75 letters with a standard deviation of 7.0 letters. This hierarchical approach for the comparison of LUMINOPIA vs VIVID VISION will be employed in all primary, secondary, and exploratory analyses.

For the PedEyeQ questionnaire, the adaptive false discovery rate (FDR) method with two-stage testing will control the FDR at 5% to adjust *p*-values and CIs for multiplicity.[52] Each treatment comparison (LUMINOPIA vs GLASSES, VIVID VISION vs GLASSES, and LUMINOPIA vs VIVID VISION) is conducted separately and will be considered a separate family of tests.

8.15 Exploratory Analyses

Exploratory analyses will test the null hypothesis of no difference between treatment groups. For any of the following exploratory analyses, if both LUMINOPIA and VIVID VISION are superior to GLASSES, then LUMINOPIA and VIVID VISION will be compared without further adjustment to the type 1 error rate. If, however, both dichoptic treatments are not superior to GLASSES, then a *p*-value for the comparison of LUMINOPIA vs VIVID VISION will not be presented.

8.15.1 Mean Change in Distance VA at 9 weeks

Change in amblyopic eye VA from baseline to 9 weeks is a continuous outcome. Analyses, including imputation of missing data, will mirror the primary outcome.

8.15.2 Mean Change in Distance VA over 18 weeks (area under the curve)

The change in amblyopic eye distance VA from baseline over 18 weeks (area under the curve) will be calculated for each participant using the trapezoidal rule. The analysis, including imputation of missing data, will mirror the primary outcome.

8.15.3 Improvement of Amblyopic-eye Distance VA by 2 or More Lines

Improvement of amblyopic-eye distance VA of 2 or more lines (reduction of $\geq$ 10 letters) at 9 and 18 weeks are binary outcomes that will be analyzed using logistic regression adjusting for baseline amblyopic-eye VA. For each time point, the proportions with improvement $\geq$ 2 lines and 95% confidence interval will be calculated. The risk difference will be calculated using logistic regression with conditional standardization, centering on the mean amblyopic-eye VA at baseline. The delta method will be implemented to construct a 95% CI on the risk difference and the model-based two-sided *p*-value will be reported.[53]. Missing data will be imputed as described for the primary outcome.

8.15.4 Resolution of Amblyopia at 9 weeks and 18 weeks

Resolution of amblyopia is defined as $\leq$0 lines IOD and fellow-eye VA no worse than 1 line (5 letters) below baseline. The cumulative probability of amblyopia resolution at 9 and 18 weeks will be calculated using Cox proportional hazards regression with adjustment for baseline IOD. For each visit, the rate of resolution (estimated using the survivor function) and 95% CI will be presented for each group using direct adjustment along with the difference in rates, 95% CI, and *p*-value (based on a Z test). Participants who are lost to follow up will be censored on the day of the last completed visit.

8.15.5 Binocular Function

The change in binocular function score from enrollment to the 9- and 18-week visits is an ordinal outcome. Components of binocularity include results from the following 3 tests: Randot Preschool Stereoacuity (RPS), Random Dot Butterfly, and Preschool Worth 4-Shape (W4S) at near. These tests will create a composite ordinal binocular function score with 9 levels.[54]

The difference between treatment groups for the change in binocularity from baseline to 9 and 18 weeks will be evaluated with the nonparametric Wilcoxon Rank-Sum test. Differences between groups will be estimated using the Hodges-Lehmann estimator with 95% CI. Analyses for binocular function score will be limited to complete case data at each respective outcome visit (9 weeks or 18 weeks).

In a sensitivity analysis, binocular function scores will be analyzed using ANCOVA with adjustment for baseline binocular function score and imputation of missing data. The baseline-adjusted mean difference and 95% CI in binocularity between the treatment groups will be presented.

8.15.6 Treatment Impact Questionnaire

The Treatment Impact Questionnaire (TIQ) will be used as a quantitative measure to evaluate opinions regarding the burdens and impact of the randomized treatment at 9 weeks and 18 weeks (as questions for the child – the Child TIQ, for the parent about the child – the Proxy TIQ, and the parent themselves – the Parent TIQ.

The Child-TIQ, Proxy-TIQ, and Parent-TIQ will undergo separate factor analysis to determine the number of domains for each TIQ. Each domain will be refined through the evaluation of misfitting items and will then be Rasch scored.

Note that because the TIQ is not administered at baseline (because treatment has not been started), there will be no adjustment for baseline score in any analysis.

Additional methods to score and analyze the Treatment Impact Questionnaire will be detailed in a separate SAP.

8.16 Dichoptic Therapy after GLASSES

Participants who were randomized to GLASSES who have 1 line or more (≥ 5 letters) IOD residual amblyopia will be offered dichoptic treatment with either LUMINOPIA or VIVID VISION after 18 weeks. These participants will be randomized to one of the dichoptic treatments and will have visits at 27 weeks and 36 weeks to evaluate safety and efficacy. The same safety, binocular function, and VA outcomes evaluated at 9 and 18 weeks will be evaluated at 27 and 36 weeks with 18 weeks considered the baseline visit for the extended follow-up.

Chapter 9: Data Collection and Monitoring

9.1 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 in real-time, 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, data not directly entered in real-time), 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.

9.2 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.

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

9.4 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 10: Ethics/Protection of Human Participants

10.1 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.

10.2 Institutional Review Boards

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

10.3 Informed Consent Process

10.3.1 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 an interpreter 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 and/or assent form(s) 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.

10.3.2 Participant and Data Confidentiality

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

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

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

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

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

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

10.3.3 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 11: References

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