

**Randomized Controlled Multicenter Clinical Trial
of Multi-Periscopic Prism Glasses for Homonymous Hemianopia**

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**IRB protocol and analysis plan
12 June 2025**

Institutional Review Board Intervention/Interaction Detailed Protocol

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Project Title:	Randomized Controlled Multicenter Clinical Trial of Multi-Periscopic Prism Glasses for Homonymous Hemianopia
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1. Background and Significance

Patients with homonymous hemianopia (HH), the loss of half the field of vision on the same side in both eyes, have difficulties navigating and avoiding obstacles (Yates et al., 2002; Chen et al., 2009; Bowers et al., 2014a). The consequent loss of mobility, increased risk of collision with other pedestrians, falls due to tripping obstacles (Freeman et al., 2007), and unsafe driving (Bowers, 2016) are detrimental to patients' independence and quality of life (Papageorgiou et al., 2007; Chen et al., 2009; O'Neill et al., 2011).

Prisms designed to shift portions of a scene from the blind field to the residual seeing field are the simplest, lightest, and most cost-effective devices for field expansion for patients with HH. Commercially available Fresnel peripheral prism (FPP) glasses (Fig. 1) have a maximum power of 57 Δ , providing about 30° of field expansion. In multicenter and laboratory-based studies, this field expansion was found to be helpful for detecting obstacles on the blind side when walking (Giorgi et al. 2009, Bowers et al, 2008; Bowers et al., 2014) and improved detection of blind side hazards in a driving simulator (Houston et al., 2018). However, current prism devices for patients with HH still have some limitations (Apfelbaum et al., 2013; Jung et al., 2014; Peli et al., 2016b; Peli et al., 2017a). In particular, currently available FPP glasses do not provide sufficient field expansion to enable detection of pedestrians approaching from a bearing angle of 45°, determined to be the bearing angle with the highest collision risk when walking (Peli et al., 2016a). Since the maximum power of currently available Fresnel prisms is only 57 Δ ($\approx 30^\circ$), these prisms fall short of covering the highest risk (45°).

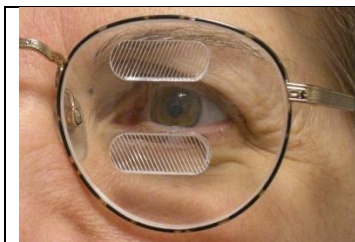


Figure 1: Commercially available Fresnel peripheral prism glasses manufactured by Chadwick Optical, shown here in front of the left eye for a patient with left HH. The 57 Δ Fresnel prism segments are embedded in the upper and lower parts of the spectacle lens with a prism-free area between. Patients look through the prism-free area while the prism segments provide expansion in peripheral vision.

To address the need for higher power prismatic devices, we have developed a new type of prismatic field expansion device for patients with HH, the “*multi-periscopic prism*” (MPP). The MPP is a specially arranged cascade of half-penta prisms (commonly used in binoculars) that provide 45° image

shift (Fig. 2a) and facilitate a wide (15°) eye scanning range (Peli et al., 2016c; Peli et al., 2018). The half-penta prisms are assembled using 3D-printed modules (Fig. 2b) and then mounted in spectacle carrier lenses as peripheral prisms (Fig. 2c). Since the MPP uses double reflections, it is free of refractive image quality effects such as distortion (minification), image dimming, and contrast reduction due to the color dispersion which limits the image quality of conventional Fresnel prisms (Katz, 2004b; Katz, 2004a). The method of use of the MPP does not differ from that of the conventional FPPs currently prescribed for patients with HH by optometrists or ophthalmologists; the MPP only provides a clearer image, wider field expansion, and facilitate 3 times wider eye scanning than is possible with the FPP. (Peli et al., 2020)

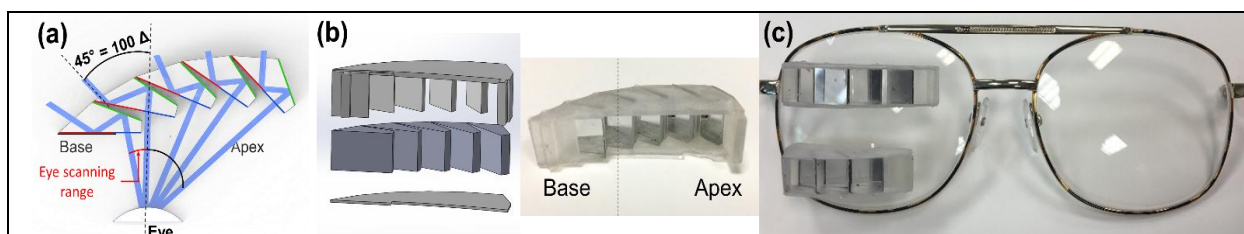


Figure 2. MPP for field expansion. (a) Optical design of MPP (cascading 5 units of 8 mm width half-penta prisms) for HH with base left. The different rays indicate visual field at 15° steps (0° to 45°) all together showing a 45° shift and permitting an additional 15° eye scanning into the blind side. (b) CAD design (left) and 3D-printed prototype (right) of MPP for HH with base left (c) A prototype of peripheral MPPs mounted for left HH (base-in). The MPPs are mounted in front of the carrier lens and thus incorporate the spectacle correction.

In early feasibility tests, prototype MPPs provided 45° (100Δ) of lateral field expansion for patients with HH, measured using a conventional visual fields test, and improved detection of pedestrians at bearing angles of 25° and 40° on the blind side in our VR walking simulator. In contrast, 30° (57Δ) FPP glasses improved detection of blind side pedestrians at a bearing angle of 25° , but not 40° . Based on these promising preliminary data we are now proposing to conduct a multi-site clinical trial to evaluate the MPPs for patients with HH.

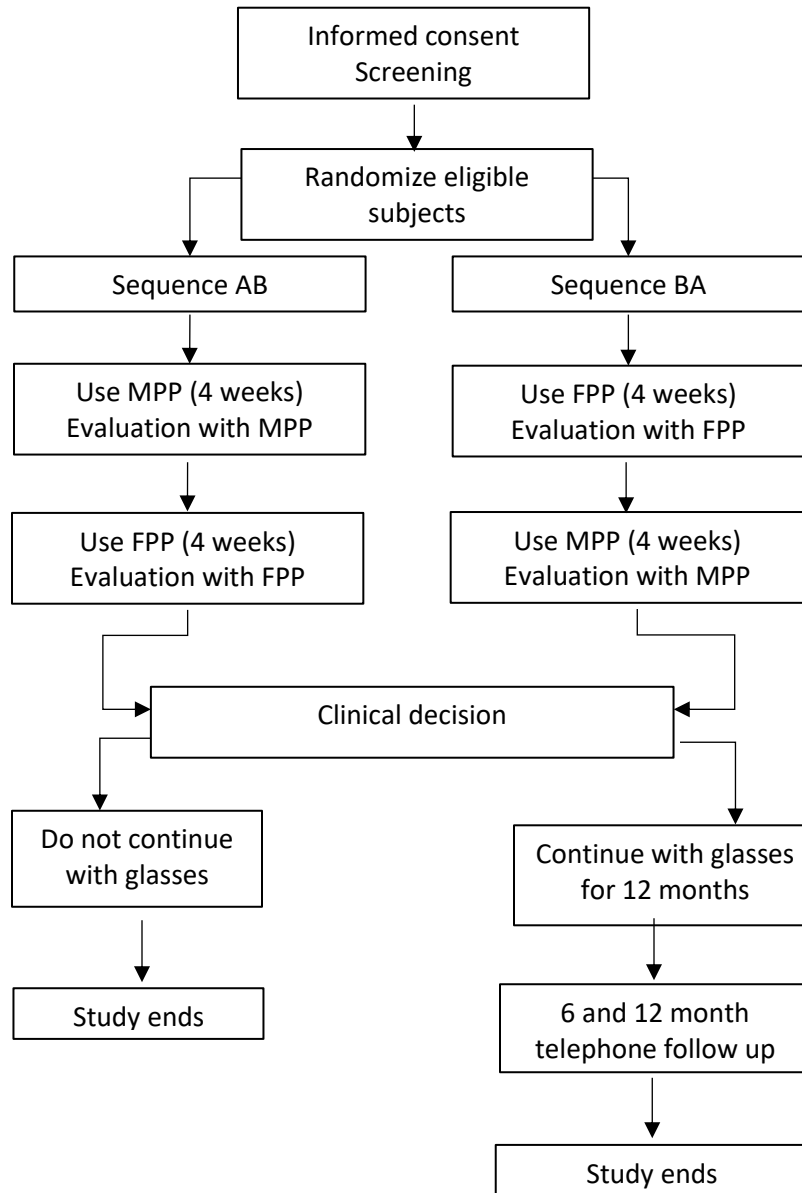
2. Specific Aims and Objectives

We will conduct a multi-center randomized crossover clinical trial to evaluate the efficacy of Multi-Periscopic Prisms (MPP) compared to conventional Fresnel peripheral prisms (FPP) as a mobility device for patients with HH. We will evaluate the ability of the prismatic devices to improve detection of moving hazards on the side of the field loss.

We hypothesize that performance will be better with the MPPs than the FPPs as evidenced by higher detection rates in the pedestrian detection and collision judgment task in our virtual reality (VR) walking simulator. In particular, we predict that the MPP will enable detection of pedestrians at much higher bearing angles on the side of the field loss and thereby protect against the higher risk for such collisions.

3. General Description of Study Design

This is a masked, randomized controlled multi-center trial (with a crossover design) to evaluate the efficacy of the MPP in comparison to the current standard of Fresnel peripheral prisms (FPP).



4. Subject Selection

Inclusion/Exclusion criteria:

- Inclusion Criteria:
 - At least 7 years of age
 - Homonymous hemianopia with or without macular sparing for at least 3 months
 - Visual acuity of at least 20/50 in each eye, with correction if needed
 - Refractive error within the -12D to +5D range
 - Able to walk independently, using a cane or walker if needed
 - Able to communicate in English sufficiently to understand the study procedures and how to use the prisms, to be determined by examiner's judgement on visit 1 (because funding is not available for interpreter services)
- Exclusion Criteria:
 - Central visual field loss in the seeing hemifield of either eye (e.g., from macular degeneration, glaucoma, diabetic retinopathy or other maculopathies)
 - Hemi-spatial neglect
 - Significant cognitive impairment
 - Dementia
 - Any other physical or mental disabilities, or general health problems that could impair the ability to be independently mobile (i.e., walk), participate in the VR walking simulator test or use the prism glasses

Recruitment sources and procedures:

The clinical trial will be conducted in two phases: a pilot phase during which participants will be recruited at Schepens Eye Research Institute and Massachusetts Eye and Ear, followed by the main phase when participants will be recruited at Mass Eye and Ear and other sites outside the MGB network. In this version of the protocol, recruitment sources and procedures are described in detail for the pilot phase at Schepens Eye Research Institute and Massachusetts Eye and Ear. Similar procedures will be used at other sites when they are added to the parent protocol.

- **Who is responsible (role on research team) for identifying and recruiting individuals**
Please see paragraphs below for details of who is responsible for identifying and recruiting participants for each of the recruitment sources.
- **When individuals are recruited**
Participants may be recruited at any time point providing it is at least 6 months since the onset of the HH.
- **Where individuals are recruited**
In the pilot phase of the clinical trial, subjects will be recruited at Schepens and Mass Eye and Ear from the following sources:

1) Vision rehabilitation clinic at MEE

Clinic staff will identify patients that meet our recruitment criteria. Clinic staff will present details about the study to potential subjects when they attend the clinic. Clinic staff will use the information sheet in our recruitment pack (described below). The potential subject can then either contact us

directly (using the contact information on the information sheet) or can complete the permission-to-be-contacted form (part of the recruitment pack described below) and give the form to a clinic staff member. Completed permission-to-be-contacted forms will be returned by clinic staff to the study coordinator. A study team member (study coordinator or research assistant) will then contact the patient by telephone about the study (Telephone script).

2) *Other ophthalmology and rehabilitation clinics in the MGB network*

This will primarily involve recruitment from rehabilitation clinics at Spaulding. Procedures for recruitment will be the same as described in (1) above.

3) *The vision rehabilitation clinic of Dr. Peli at Tufts*

Dr. Peli's clinic at Tufts is outside the MGB network. However, Dr. Peli holds appointments at both Tufts and Schepens. (Please see the uploaded letter from the Department Chief at Tufts in support of recruitment from Dr. Peli's clinic at Tufts). The methods for recruitment are similar to those described in (1) above. Dr. Peli will identify patients that meet our recruitment criteria. Then either Dr. Peli or the receptionist at the front-desk assisting in Dr. Peli's clinic will inform eligible patients about the study after the patient completes their appointment at Dr. Peli's clinic. Eligible patients will be given the information sheet from the recruitment pack. They can then either contact us directly (using the contact information on the information sheet) or can complete the permission-to-be-contacted form and return it to Dr. Peli (or the staff at his clinic's front desk who will forward it to Dr. Peli). Dr. Peli will then give it directly to study staff at Schepens.

4) *Using personalized letters mailed to patients found using the RPDR*

We will use the RPDR database to screen subjects who have not opted out of receiving information about suitable studies. We will query the database to include patients from any hospital site in Massachusetts that is included in the database. Patients with an ICD code of Homonymous Hemianopia who are alive and do not have ICD codes of other physical or cognitive disabilities or visual impairments listed, and do not have interpreter services mentioned on the list will be contacted first. We will begin by contacting 100 subjects in chronological order from most recent to older encounter dates. The research assistant on the study team will use the RPDR database to query this data. Dr. Alex Bowers will be the workgroup leader and approve these requests to receive mailing information of potential subjects to contact. Personalized letters will be mailed out to these potential subjects. (Recruitment letter attached). Persons responding with interest in learning about the study can contact the research assistant or study coordinator on the phone and they will use the telephone script (attached) to explain the study to the participant.

5) *Subjects who participated in prior studies in Dr. Peli's lab*

Subjects with HH may also be recruited from the pool of volunteers who have previously participated in studies in Dr. Peli's lab and who have given their permission to be contacted about future studies. Contact information for subjects interested in participating in future studies is held in a secure database on the network. Participants identified from this database will be contacted directly by phone by the coordinator or the research assistant from the study to tell them about the study. (Telephone script)

6) *Study listing on websites and social media:*

In addition, we might list our study on social media platforms relevant to patients with hemianopia. We will contact the host of each platform and request that information about our study be listed

and, if possible, that chat and comment features be disabled. Participants recruited in this fashion will contact us directly either by phone or by using our recruitment email address. Potential participants who respond to this study listing will then be contacted directly by phone by a study team member (Telephone script). In the interest of privacy/confidentiality, there will be no interaction or answering of questions via posts and/or commenting features on the platforms.

- **Recruitment Pack**

The pack includes an information letter for the practitioner, an information sheet about the study for the patient and a Permission-to-be-contacted form for disclosure of the subject's contact information. Potential participants can either complete the Permission-to-be-contacted form which will be returned to the study coordinator by the healthcare provider, or the patient can contact the study coordinator directly by phone. The coordinator or research assistant from the study will call patients who complete the contact form and give them further information about the study and will schedule a screening visit if the person is interested in participating. (Telephone script attached)

- **Methods to reduce risks of coercion or undue influence**

For participants who are among Dr. Peli's own patients, the risks of coercion or undue influence will be minimized by having one of the study staff contact the patient about the study upon receiving a permission-to-be-contacted form and give them further information about the study. If the potential subject has additional questions about the study, then they can talk with co-investigator, Dr. Bowers, who is an optometrist (licensed to practice in the UK). Thus Dr. Peli will be directly involved when one of their patients is making a decision about whether to participate in the study.

- **How recruitment goals match the prevalence rates of the condition/disease being studied and the populations most impacted by the condition/disease being studied?**

Hemianopia affects both genders and members of all racial and ethnic groups. Therefore, during this study, no individuals will be excluded based on race, ethnicity or gender, and every attempt will be made to ensure that minorities and women meeting the eligibility criteria are recruited for participation. It is expected that approximately equal numbers of males and females will be recruited. There are some racial/ethnic group differences in the prevalence of certain diseases that cause hemianopia and we expect that this will be reflected in the sample populations that we recruit.

- **Methods to enhance enrollment of diverse individuals and under-represented populations**

We are not proposing any specific outreach programs for recruiting specific gender, racial and ethnic groups, as all eligible participants will be recruited regardless of gender, race and ethnicity.

5. Subject Enrollment

Pre-screening

Subjects will not be prescreened

Consent process:

- **When and where informed consent will be obtained**

Informed consent will be obtained at the start of the first visit. Consent procedures will be conducted in a quiet, private area at the study site by a trained member of the study team. Before the first visit all potential participants will be given an opportunity to receive a copy of the consent

form (by email or mail). During the subject's first visit, the research assistant or site-specific staff administering the consent forms will discuss the forms on site and address any concerns related to the study procedures. Subjects will be given ample opportunity to discuss all aspects of the study and ask questions before signing the form. The forms will be signed by the subject on-site only. However, subjects are not obligated to sign the form on the same day and may choose to take time to decide before signing the forms.

- **Consent process for minors and children**

In the case of minors (age <18 years old), at least one parent or guardian will undergo the consent process with the subject and will be requested to sign the consent form. The subject will sign the consent form (age ≥ 14 years) or child assent form (7-13 years) as appropriate for the age. If a subject turns 18 years of age while taking part in this study, we will ask them to sign a new consent form at that time.

- **The process for obtaining consent from non-English speakers if applicable**

N/A

- **The process to determine capacity to consent and use surrogate decision makers if applicable**

N/A

- **Procedures to minimize undue influence to enroll investigators' own patients**

If a participant is a patient of one of the investigators, that investigator will not be directly involved in the consent process and will not be in the room during signature, to prevent any sense of pressure/coercion.

- **Post-consent intervention assignment and randomization method**

Participants who meet the eligibility criteria will be randomly assigned to sequence AB or BA. The allocation will be performed using software that implements the process of minimization. In minimization, the first participant is assigned randomly with each subsequent participant assigned in such a way as to approximately balance the two sequences for age and study site. Letter codes, randomly assigned to each of the treatment allocations by Dr. Jae-Hyun Jung, will be used by the software. The code breaker will be kept in a sealed envelope in a locked file cabinet in one of Dr. Jung's rooms at Schepens. Dr. Jung is a member of the study team who is neither involved in data collection nor statistical analysis of the data. Data provided to the masked person conducting statistical analyses will use the letter codes to identify treatment allocation.

6. Study Procedures

Study devices

Fresnel peripheral prism glasses and multi-periscopic prism glasses will be supplied for each subject.

- **Fresnel peripheral prism glasses (FPP)**

FPP glasses (Fig. 1) comprise Fresnel prism segments embedded as peripheral prisms in a prescription carrier lens, providing about 30° image shift. FPP glasses, known as the "Peli lens", are commercially available from Chadwick Optical. They will be manufactured by Chadwick Optical for the study participants, including their individual prescription for spectacles.

- **Multi-periscopic prism glasses (MPP):**

MPP glasses (Fig. 2) comprise a series of half-penta prisms (commonly used in binoculars) that provide 45° image shift. The half-penta prisms are assembled using 3D-printed modules and then mounted in spectacle carrier lenses as peripheral prisms. MPP glasses will be assembled by Chadwick Optical for study participants, including their individual prescription for spectacles.

- **Method of administration**

The FPP and MPP glasses manufactured by Chadwick Optical will be sent directly to the study sites and stored in a secure location at each site. Prism glasses will be fitted to subjects by study staff at each site. Each pair of prism glasses is unique and can only be used by the subject for whom they were made. There will be no re-use of prism glasses by other subjects. After a subject finishes study participation, any study glasses not being used by the subject will be returned to Chadwick Optical for recycling.

Description of each study visit and procedures, and schedule of assessments

The following provides a summary of each visit and procedures. The timing of each visit is summarized in Table 1. The majority of data collection will be performed using standard clinical tests or questionnaires. The virtual reality (VR) walking simulator test, which will be the main outcome measure for the clinical trial, is described in detail below. Other standard clinical tests are not described in detail.

- **Visit 1: Screening and measurements for prisms**

- Informed consent
- Visual acuity
- Visual fields
- Tests for hemispatial neglect (Bells test and Schenkenberg Line Bisection)
- Test of cognitive status (Short portable mental status questionnaire)
- Ocular and other relevant history
- Ocular examination (or ocular examination within prior 6 months)
- Refraction to verify spectacle prescription (or refraction within prior 3 months)
- Clinical tests of binocular status (as necessary)
- Fitting measurements for prism glasses including use of a photograph: After selecting a suitable spectacle frame for the subject a photo will be taken for reference measurements (the photo will only show one eye and the frame around that eye; Figure 3).

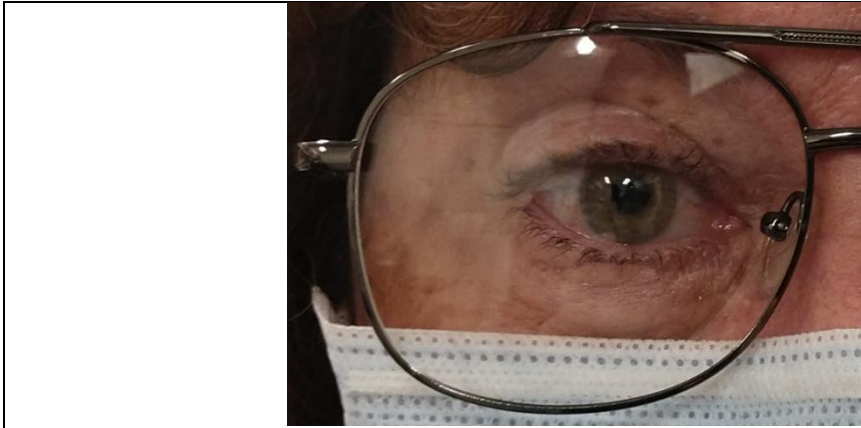


Figure 3: A reference photo to document the location of the pupil with respect to the frame. The person taking the photo will zoom in as much as possible so that the photo includes only the eye and frame on the side that the prisms will be fitted. If needed, the photo will be cropped to exclude any other facial features. Only the cropped photo will be stored. This photo will be referenced with the subject's study ID code and included with the order for prism glasses sent to Chadwick Optical by study staff at Schepens

- **Eligibility determination**

After Visit 1, study staff at Schepens, supervised by Dr. Peli or Dr. Bowers, will review the results of the screening tests and make a decision about eligibility. Eligible participants will then be assigned to sequence AB or BA using minimization by a member of the study team at Schepens and the study site will be informed.

- **Manufacture of prism glasses**

A pair of FPP glasses and a pair of MPP glasses will be manufactured for each eligible participant by Chadwick Optical. Schepens will prepare the order for prism glasses based on the measurements taken at Visit 1 and send the order directly to Chadwick, including the reference photo to document the location of the pupil with respect to the frame. After manufacture, study glasses will be sent by Chadwick Optical to the study site. Study ID codes will be used on all orders for prism glasses (participant names will not be used). We anticipate that it will take about one month for the study glasses to be manufactured and sent to the study sites.

- **Visit 2: Fitting first pair of prism glasses**

- Mobility questionnaire (rate level of difficulty in various situations without prism glasses)
- Fit first pair of glasses
- Photo to document fitting of first pair of prism glasses (includes only the eye and frame on the side the prisms are fitted)
- Training in how to use the first pair of glasses, including a walk through corridors and rooms, accompanied by a member of the research team
- VR walking simulator test (practice without prism glasses)

- **Home use - first pair of prism glasses**

Subjects will use the first pair of prism glasses in everyday mobility as much as possible for about four weeks. They will receive a telephone call about one week after visit 2 to review how they are using the prism glasses, answer any questions they may have, and check for any adverse events that might have occurred.

- **Visit 3: Evaluation of performance with first pair of prism glasses and fitting second pair**

- Visual fields (without and with first pair of glasses)
- VR walking simulator test (without and with first pair of glasses, order counterbalanced)
- Mobility questionnaire and device questionnaire (for first pair of glasses)
- First pair of glasses will be retained at the study site
- Fit second pair of prism glasses
- Photo to document fitting of second pair of prism glasses (includes only the eye and frame on the side the prisms are fitted)
- Training in how to use second pair of glasses including a walk through corridors and rooms, accompanied by a member of the research team

- **Home use - second pair of prism glasses**

Subjects will use the second pair of prism glasses in everyday mobility as much as possible for about four weeks. They will receive a telephone call about one week after visit 3 to check that they are using the prism glasses, answer any questions they may have and check for any adverse events that might have occurred.

- **Visit 4: Evaluation of performance with second pair of prism glasses and clinical decision**

- Visual fields (without and with second pair of glasses)
- VR walking simulator test (without and with second pair of glasses, order counterbalanced)
- Mobility questionnaire and device questionnaire (for second pair of glasses)
- Comparison questionnaire (compare two pairs of prism glasses)
- Clinical decision by practitioner about whether subject should continue with MPP, FPP or no prisms (based on practitioner's clinical judgment, subject's preference and if performance with the prism glasses is not worse than the performance without the prism glasses during the study visits).

- **Optional extended wear with long term follow up**

Subjects who have a clinical decision to continue and wish to continue with either the MPP or the FPP glasses will be invited to participate in the extended wear phase of the study. Participants in the extended wear phase will receive a follow up telephone call about 6 months after Visit 4 and again about 12 months after Visit 4 to determine whether they are still using the prism glasses. If a subject is having difficulties with the prism glasses during the extended wear phase, a study visit to review the problems will be arranged if necessary. Otherwise there will be no in-person study visits during the extended wear period.

If a subject is interested in continuing with prism glasses, but not willing to participate in the telephone follow ups, they will not be able to participate in the extended wear trial and the study team will retain both pairs of prism glasses. (They could, however, be fitted with prism glasses by their eye doctor outside of the study as part of clinical management of their condition). Based on

prior experience, we believe that it is highly unlikely that a subject who wants to continue with either the FPP or MPP glasses will not be willing to receive the follow-up phone calls. Completion of the extended wear part of the study is the best way for us to determine whether it is appropriate for the subject to continue to wear prism glasses in the long term.

We believe that this is in the participant's best interests. Based on prior experience of two multi-site trials of the FPP glasses for hemianopia, it is highly unlikely that a participant who wants to try the prism glasses in the longer term would not be willing to participate in the extended wear part of the study, which involves only 2 telephone calls.

There will be no long term follow up for subjects who do not have a clinical decision to continue with either the MPP or FPP glasses.

At the end of study participation, all subjects will return to the routine care of their eye doctor.

Rationale for permitting subjects to keep glasses only after the end of the extended wear period: By the end of the crossover period, participants will only have worn each pair of prism glasses for 4 weeks. This is a relatively short period of time. It is long enough to evaluate whether it is clinically appropriate for them to continue with prism glasses in the extended wear phase of the study, but not long enough to determine whether they should continue with glasses in the long term. It is only after participants have worn prism glasses for an extended period (more than 4 weeks) that we will be able to fully determine whether they should continue to use glasses in the long term after the end of the extended wear part of the study. Therefore, participants will only be permitted to keep glasses after the end of the extended wear part of the study.

Table 1: Schedule of visits and assessments

	Visit 1	Visit 2 Day 1	1-week follow up Day 8 ± 3	Visit 3 Day 29 ± 7	1-week follow up Day 36 ± 3	Visit 4 Day 57 ± 7	6 month follow up Day 225 ± 21	1 year follow up Day 393 ± 21
Informed Consent	X							
Visual acuity	X							
Visual fields without prism glasses	X			X		X		
Visual fields with prism glasses				X		X		
Neglect tests	X							
Cognitive status test	X							
Ocular and other relevant history	X							
Ocular examination	X							
Refraction	X							
Binocular status tests	X							
Measurements for prisms with photo	X							
Fit and train in use of prism glasses		X		X				
Photo to document fitting of prisms		X		X				
VR walking simulator practice		X						

Mass General Brigham Institutional Review Board
Detailed Protocol

	Visit 1	Visit 2 Day 1	1-week follow up Day 8 ± 3	Visit 3 Day 29 ± 7	1-week follow up Day 36 ± 3	Visit 4 Day 57 ± 7	6 month follow up Day 225 ± 21	1 year follow up Day 393 ± 21
VR walking simulator data collection				X		X		
Mobility questionnaire		X		X		X		
Device questionnaire				X		X		
Comparison questionnaire						X		
Clinical decision on keeping glasses						X		
Telephone follow up			X		X		X	X

Data collection methods and variables

- **Clinical tests and questionnaires**

At each visit, results of clinical tests and responses to questionnaires will be recorded by study staff at each site on the relevant data collection sheets (included as attachments). Electronic scanned copies of the data sheets will subsequently be sent to Schepens by secure data transfer for review and analysis.

- **VR walking simulator**

Each study site will have an identical set up for the VR walking simulator, comprising a large TV screen and a laptop computer with test software installed (Fig 4). Subjects will be asked to stand (or sit) in front of the TV screen. For subjects who stand, there will be a high walking frame to provide support and help maintain the correct position (Fig 4). A video that simulates walking through a busy mall with other pedestrians will be displayed on the TV screen (Fig 4). Subjects will watch the video and push a joystick when they see a pedestrian which might collide/walk into them (push the joystick in the direction from which the pedestrian is approaching). They will also be asked to perform a task to control gaze location, which will involve looking at a fixation target and calling out occasional numbers within a string of letters they see displayed on the fixation target (Fig 5). Subjects will have an opportunity to practice the tasks before experimental data collection commences. Each video will be about 4 to 5 minutes in duration and subjects will be able to take a break whenever they need to. Data from the VR walking simulator (e.g., timing of button press responses) will automatically be recorded as numeric data by the software and saved in an electronic file, which will subsequently be sent to Schepens by secure data transfer to which only the study personnel will have access. Performance will primarily be quantified in terms of detection rates for colliding pedestrians and response times (from pedestrian appearance to the button press response). Other variables, such as the distance of the pedestrian at the time of the button response, might also be computed.



Figure 4: VR walking simulator set up with large TV screen on a height adjustable table and a high walker with arm rests for support. Joysticks (to record participant responses) are mounted on the ends of the arm rests.

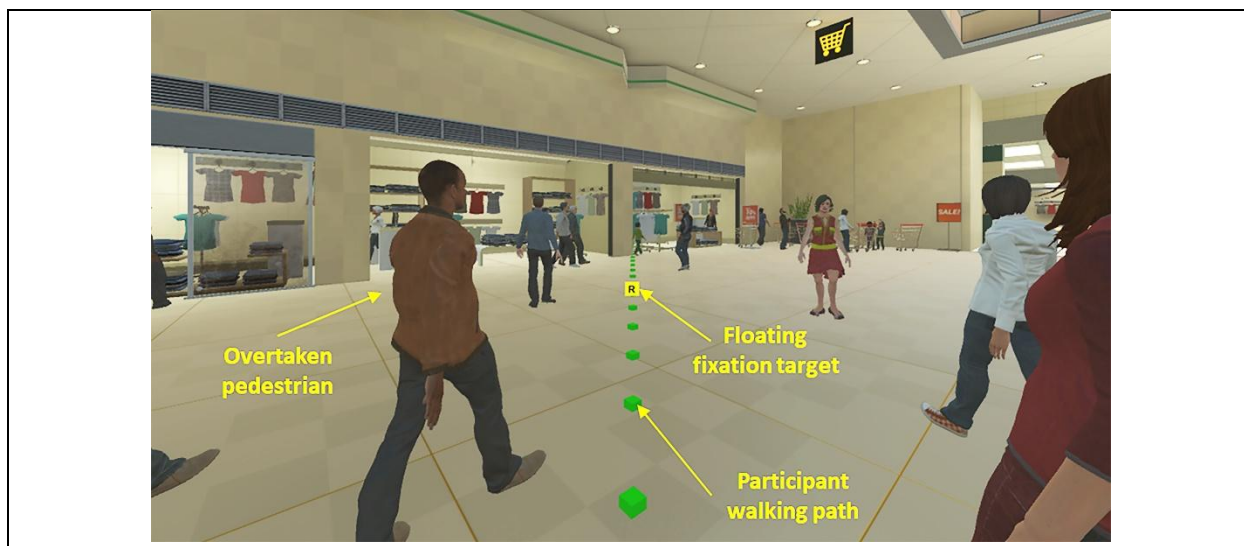


Figure 5: Sample screen shot of a VR walking simulator video from the participant's perspective (spanning 110° horizontally) showing multiple pedestrians walking in a virtual shopping mall. The participant's walking path is denoted by the green markers on the floor. There is an overtaken colliding pedestrian on the left and multiple non-colliding pedestrians on both sides. In this example, the participant would be asked to call out numbers that appear in the yellow square at the gaze point, as well as to push the joystick when they see a pedestrian likely to collide with them. When looking straight ahead without the prism glasses, a participant with HH will see the scene on only one side of their walking path.

Plans for return of research results

There are no plans to return research results to subjects at the end of the study. If subjects indicate an interest in the outcome of the study, a note-to-file will be made, and the PI may share the final published manuscript with these study participants.

Primary and secondary outcomes

- **Primary outcome measure:** Our primary outcome measure will be the improvement (binary, yes/no) in collision detection with prism glasses for pedestrians approaching from the blind side at a bearing angle of 40° (within the expansion range of MPPs but not FPPs). Improvement will be defined as blind-side detection rates that are significantly higher with than without prisms at the same visit ($p < 0.05$; z-test for two proportions) for correct detections with a timely response (more than 1 second until the collision point).
- **Secondary outcome measures:** The secondary outcomes will include 1) improvement in detection with prism glasses for pedestrians approaching from the blind side at a bearing angle of 20° (within the expansion range of MPPs and FPPs), and 2) responses to the comparison questionnaire addressing device preference and comparison of the two devices for specific attributes such as helpfulness for obstacle avoidance and cosmetic appearance. We have included patient preference as one of the secondary measures because it reflects each patient's self-determination of device efficacy based on their perception of device functionality in everyday mobility.

Study termination criteria

Study participation will be terminated and the prism glasses will be retained by the study team if:

- It becomes apparent that the subject is having difficulties with the prism glasses that could endanger the subject or others;
- The subject no longer meets the inclusion criteria (e.g., becomes unable to walk during the course of the study);
- The subject experiences a serious adverse event;
- The subject reports any risky behavior while wearing the glasses such as driving or operating heavy machinery.

Local site restrictions or site-specific procedures:

All sites will use the same procedures.

Description of what happens to participants when the study ends or if a participant's participation in the study ends prematurely.

At the end of the study, subjects will return to the routine care of their own eye doctor. If a subject's participation ends prematurely, they will return to the routine care of their own eye doctor.

Remuneration

Subjects will not be reimbursed for time participating in study visits but will be reimbursed up to \$50 per visit for transportation to Schepens Eye Research Institute/Mass. Eye and Ear.

However, they will be permitted to keep one pair of prism glasses (that cost about \$1000) at the end of the extended wear phase, if considered clinically appropriate. (Subjects who do not complete both periods of the crossover will be requested to return the prism glasses to the site.)

Plans for receiving data from research collaborators outside Mass General Brigham

In the first phase of the clinical trial (pilot data collection at Schepens and Mass Eye and Ear), data will not be received from collaborators outside of Mass General Brigham. Once the multi-site sIRB protocol is implemented, data will be received from research collaborators outside MGB and will be transferred via a secure method (e.g., MGB Dropbox Business). All of the experimental data will be de-identified and will be labeled using only the subject's study ID code. Only consent forms will have identifiable information. Consent forms will be electronically scanned, attested by the site personnel to be a true copy and sent to Schepens by the secure transfer method.

Masking

- Only the person conducting the statistical analyses will be masked to treatment allocation.
- Study participants will not be masked as it would be impossible to do so. (Information about FPPs is readily available on the internet so they could easily determine which pair of prism glasses was already commercially available).
- Study team members fitting prism glasses, training participants to use prism glasses, and performing data collection will not be masked as it would be impossible to do so. These team members will all be knowledgeable about prism glasses and will easily be able to see whether participants are using the MPP or FPP glasses; the prism glasses have to be worn during data collection for the primary outcome measure. Given that the primary outcome measure is based on objective electronic data (rather than questionnaire data), we believe the risk that data collectors might bias the results is very low. (The primary outcome measure is based on performance in the VR walking simulator pedestrian detection task. Electronic data collected while the participant performs the test will be sent directly to Schepens for processing to derive the primary outcome measure.)

7. Risks and Discomforts

All procedures in this study are minimal risk.

Vision Tests: These are regularly performed for most eye exams.

Prism glasses: There are some risks associated with using the prism glasses, but these are similar to the risks encountered when first wearing bifocal or progressive addition lenses. There may be a period of adjustment to the use of the new prism glasses during which the subject may find mobility more difficult and he/she may experience some discomfort. These risks are minimized by fitting the prism glasses while the subject is seated, taking subjects for a supervised walk so that they can get used to the prism glasses before they take them home, providing take-home instructions on how to use the prism glasses, advising subjects to start by using the glasses in a familiar environment, advising subjects to always carry their regular glasses with them so that they can take the prism glasses off and wear their regular glasses if the prism glasses make them feel uncomfortable in any situation, and advising subjects not to drive or operate heavy machinery when wearing the prism glasses.

VR walking simulator pedestrian detection task: There is a slight risk that some people may experience slight and temporary motion sickness from viewing video backgrounds with simulated motion. There will be programmed breaks in testing sessions, which will help to reduce the risk of motion sickness, and subjects will be able to take a break at any time if they become uncomfortable.

Confidentiality: Procedures to minimize risks to confidentiality include recording demographic and contact information on a separate form from the rest of the experimental data, storing in locked file cabinets all forms or records with information about a subject that would allow identification, and the use of unique subject identifier codes on all experimental research data forms and electronic data files. Any electronic data files that would allow subject identification will be password protected on a secure server at each site. Except for the consent form, all data transferred from the clinical sites to Schepens will be de-identified and will be transferred via a secure method. Any photographs taken of the subject to verify the position of the frame on the face will include only one eye and the position of the frame around that eye (i.e., the photo will be de-identified). Other facial features or the full face will not be photographed. Each site will be provided with a mobile phone to capture the photo. The phone will not be connected to any internet or mobile networks. The study personnel will transfer the photo to a PowerPoint slide with instructions to crop unnecessary identifiable information that may inadvertently be included in the photo and only save the cropped version. Each site will be provided with a laptop encrypted at MGB which will be used to run the software and log the data for the VR walking simulator test.

8. Benefits

Potential Benefits to Participants: Subjects will get to take home and try two pairs of prism glasses (retail cost of \$1000 or more for each). The glasses may help them to detect and avoid collisions with obstacles when walking resulting in safer mobility during everyday activities. At the end of the study, they may be allowed to keep one pair of glasses, if clinically appropriate, which may continue to help them in the longer term to detect obstacles when walking.

Potential Benefits to Society: Demonstrating efficacy of the MPP glasses will give patients with HH access to a new type of glasses having much better image quality and greater expanded field of view compared to those currently in the market. We expect that the use of these glasses will help patients with HH detect obstacles on their blind side and therefore aid safer mobility in everyday situations.

9. Statistical Analysis

Data analysis plan

The differences in blind-side detection improvement rates between MPPs and FPPs will be analyzed using a McNemar test for data combined across both periods of the crossover, testing the hypotheses that improvements rates will be higher with MPPs than with FPPs at the 40° bearing angle (primary hypothesis) but will not differ at 20° (secondary hypothesis). An intention to treat analysis will be used. Participants who withdraw after treatment allocation but before the end of the crossover will be categorized as no improvement for both types of prism glasses. Questionnaire responses will be analyzed with non-parametric statistics. An α -value ≤ 0.01 will be considered to indicate statistical significance for the primary analysis and ≤ 0.05 for the secondary analyses

Sample size estimate:

The sample size calculation is based on results from a small pilot study ($n = 6$) conducted in Dr. Peli's lab at Schepens in which participants with hemianopia completed measurements of collision detection using the same test as in the clinical trial. The sample size is computed for the primary outcome based on a McNemar test for a 2-by-2 contingency table of the binary improvement (yes/no) for MPPs and FPPs for detection of 40° pedestrians with data combined across both periods of the crossover. In the lab-based pilot study, 100% of participants improved with MPPs for the 40° pedestrians and 33% improved with FPPs. For the clinical trial, we anticipate that some participants will not show improvement with MPPs, and the overall effect size will be smaller. We therefore estimate that 70% of participants will improve with MPPs and 25% will improve with FPPs. The minimum sample size to detect a 45% difference between the proportion of participants improving with MPPs and FPPs is 36 participants, assuming 20% overlap (i.e. improved with both MPPs and FPPs), power of 90% and significance (alpha) level of 1%, 2-tailed test. Allowing for 30% failing to meet inclusion criteria and 20% attrition after starting the clinical trial, we estimate a total sample size of 54 participants.

Based on prior multi-site clinical trials of prism glasses for HH (Bowers et al., 2014), we expect that up to 30% of enrolled participants may fail to meet the inclusion criteria and 20% may withdraw after treatment allocation. Therefore, we will need to enroll at least 55 participants in total (as screening is done at the first visit). In addition, prior to the main clinical trial, we plan to conduct a pilot of the clinical trial at Schepens and Mass Eye and Ear to verify study procedures and generate data to verify the sample size calculation. We plan to enroll 10 participants for the pilot clinical trial. Therefore, the total enrollment will be 65 participants.

10. Monitoring and Quality Assurance

Adverse event criteria and reporting procedures

Criteria to define adverse events:

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

- **Serious adverse event** means any event temporally associated with the subject's participation in research that meets any of the following criteria:
 - results in death;
 - is life threatening (places the subject at immediate risk of death from the event as it occurred);
 - requires inpatient hospitalization;
 - results in a persistent or significant disability/incapacity; or
 - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical intervention to prevent one of the outcomes listed above.

Unanticipated Problems:

Any incident, experience, or outcome that meets all of the following criteria:

- It is unexpected (in terms of nature, severity (see severity grades below), or frequency) given (a) the research procedures that are described in the protocol-related documents, such as protocol and informed consent documents; and (b) the characteristics of the subject population being studied;
- It 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); and
- It suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Reporting Adverse events:

All adverse events whether serious or non-serious, expected or unexpected, will be reported as soon as possible to the PI (Dr. Peli) or co-PI (Dr. Bowers) - by a subject or member of the research team.

They will promptly review documented adverse events to determine 1) if the event should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

Dr. Peli (PI) and Dr. Bowers (co-PI) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study device.

All AEs will have their relationship to the study device assessed. The PI will determine the AE's causality based on the temporal relationship and his/her best judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Possibly Related** – There is some evidence to suggest a causal relationship. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Not Related** – There is no reasonable possibility that the study device caused the event, there is no temporal relationship between use of the study device and event onset, or an alternate etiology has been established.

The severity of a non-serious, unexpected adverse event will be graded as follows:

- **Mild adverse event** – Events that do not interfere with the participant's daily activities.
- **Moderate adverse event** – Events result in a low level of inconvenience or concern with the use of the glasses. Moderate events may cause some interference with regular activities related to mobility.
- **Severe adverse event** – Events interrupt a participant's usual daily activity but not potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". (For example: A person suffering a temporarily incapacitating injury such as a sprained ankle due to slipping on snow while wearing the prism glasses, even though the fall was not caused due to wearing the glasses)

Any adverse events that are serious, unexpected and related or possibly related to the study will be reported to the Mass Eye and Ear IRB within 7 calendar days from the time the PI becomes aware of the event. Any unexpected and study-related death will be reported to the Mass Eye and Ear IRB within 24 hours of the PI's knowledge of the event by e-mail or telephone. If there is any doubt as to whether an incident or observation is an AE, the event will be reported to IRB nevertheless based on the schedule described below.

The PI will report events to the IRB based on the following schedule:

- Possibly, Probably, or Definitely Related Expected AE – Report to IRB on annual basis
- Possibly, Probably, or Definitely Related Expected Serious AE – Report to IRB within 7 days
- Possibly, Probably, or Definitely Related Unexpected AE – Report to IRB within 30 days of event
- Possibly, Probably, or Definitely Related Unanticipated Problem – Report to IRB within 7 days of event (24 hours for death or data loss)
- Possibly, Probably, or Definitely Related Unexpected Serious AE – Report to IRB within 7 days of event (24 hours for death)

Unanticipated Problem Reporting

All UAPs involving risks to subjects or others will be reported to the Mass Eye and Ear IRB within 7 calendar days from the time the PI becomes aware of the event. If a UAP or an unexpected Serious AE results in a subject's death or was potentially life-threatening, the PI will notify the Mass Eye and Ear IRB

through e-mail or phone within 24 hours from the time the event is identified. A follow-up report will be submitted if applicable, at a later date when more information is available. For UAPs that result in data loss the PI will notify the Mass Eye and Ear IRB through e-mail or phone within 24 hours from the time the UAP is identified.

Planned safety monitoring

The subjects in this study will not be participating in any activities that they would not otherwise participate in as a part of their daily life. The subjects are not expected to be exposed to any potential risks other than those commensurate with the fitting of prismatic devices in a regular low vision clinic. No irreversible effects of using prism glasses or effects related to the duration of use of the glasses have been reported in our experience so far. Given the minimal risk involved in participating in the study and the nature of the use of these glasses, the study will be primarily monitored for safety by the PI. An external safety monitor (Dr. Lotfi Merabet, OD, PhD, MPH) will also be appointed. Schepens Eye Research Institute will act as the data and safety monitoring center for the study.

Monitoring for Off-site Adverse Events (Solicited and Unsolicited)

The subjects will be instructed to report any adverse events to the study personnel through telephone or email as soon as they occur (Unsolicited report). The study personnel will interview the subject for the occurrence of any adverse event while wearing the prism glasses at home during the telephone follow-up (One week after providing the glasses) or during the return visit to the clinic (After 4 weeks of using the glasses). Events reported by the subject during these interviews will be noted as solicited adverse events. Personnel preparing the study safety logs will screen for double reporting of solicited/unsolicited events.

Internal monitoring:

Study sites will submit source data and data collection sheets to Schepens by secure file transfer after each subject visit (please see Description of Data management methods below). Internal monitoring of the source data documentation, completion of data sheets, protocol adherence, recording keeping will be carried out weekly by a research assistant (or other study team member) at Schepens under the supervision of Dr. Peli (PI) and Dr. Bowers (co-I). The research assistant will also note any documented AEs or UAPs. AEs or UAPs that occur on-site will be noted in the subject's data sheets. Additionally, a separate monitoring log of expected and unexpected events and any solicited or unsolicited AE report, will be kept and sent to the PI on a case-by-case basis (usually within 24 hours of the event occurrence). This monitoring log will be stored electronically. Non-compliance with protocol (e.g., failure to use the study checklist, complete data sheets correctly, or properly document or report in a timely manner adverse events) will be documented. Once identified, minor issues will be addressed by the PI by special meeting or at weekly study meetings. Special meetings may be called depending on the seriousness of the issue. Repeated offenses will result in removal of that study staff from the protocol. Adverse events will be documented and reported to the IRB and NEI per the schedule described in the protocol.

Outcomes monitoring, including planned frequency of review.

Data summaries will be produced by the research assistant (including data on topics such as subject enrollment, withdrawals, primary outcome measures, and any safety issues) and reviewed by the PI and other study personnel during weekly study meetings. Approximately once a quarter, data summaries will be reviewed by an internal committee comprising the PI and members of the research team at Schepens to monitor data quality, primary outcomes and study progress.

Internal Data Safety Monitoring Committee and External Safety Monitor

The PI will be the primary safety monitor for this study. An internal data safety monitoring committee consisting of the PI, co-investigator (Bowers) and other members of the study team at Schepens will periodically review the study reports internally as mentioned above. Additionally, an external safety monitor, Dr. Lotfi Merabet, OD, PhD, MPH, who has no conflict of interest with the study will be appointed (please see uploaded letter and CV). Dr. Merabet is a clinician-scientist with specialist expertise in rehabilitation of patients with brain injuries and clinical trial experience. He will review safety monitoring reports prepared by the research assistant about twice a year. These reports will include data on aspects such as subject enrollment (numbers screened and enrolled), subject losses (numbers withdrawn or lost to follow up), data form completion, clinical outcomes (number of subjects advised to continue with the study devices, or to continue without devices after completion of the study), and any safety issues.

Study stopping rules as applicable

There are no study stopping rules (other than the criteria for terminating a subject from the study, detailed in the section on study termination criteria above)

Independent monitoring of source data as applicable:

Not applicable

Description of data management methods:

Data collection sheets will be completed for each subject enrolled into the study. Data collection sheets will be study visit specific and the study personnel preparing the weekly summaries for the PI will review the data sheets for completeness and document any minor protocol deviations.

Subjects will be identified by a unique study ID code that will be used on all data sheets and electronic data files. Links between study ID codes and subject identifiers will be kept in a separate secure document in a secure location at the site where the subject was recruited. The code that links information that can identify the participant to the data collected for this research will be kept separate from their health information and will be destroyed once this study is complete and all manuscripts have been published.

When study sites outside the MGB network are added to the protocol, personnel at the sites will scan de-identified datasheets and transfer them to Schepens using a secure file-sharing system that only the study team will have access to. Any deviations from protocol will be documented on a deviation log and communicated with the study site. All computer-generated data will be de-identified and shared using the approved file sharing system along with the data collection sheets. Only the PI and researchers specific to this study who have been granted access to the data by the PI will be able to view the data.

Originals of consent forms will be kept in a secure location at each site. Electronic scanned copies of consent forms, attested as true copies by study personnel, will be sent to Schepens by the secure transfer method.

11. Select the Privacy and Confidentiality measures that apply to this research:

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected

- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

12. References

- Apfelbaum, H. L., Ross, N. C., Bowers, A. R., & Peli, E. (2013). Considering apical scotomas, confusion, and diplopia when prescribing prisms for homonymous hemianopia. *Translational vision science & technology*, 2(4), 2-2.
- Bowers, A. R. (2016). Driving with homonymous visual field loss: a review of the literature. *Clinical and Experimental Optometry*, 99(5), 402-418.
- Bowers, A. R., Houston, K. E., Goldstein, R. B., & Peli, E. (2014). Peripheral prisms and training improve detection of pedestrians by drivers with hemianopia. *Investigative Ophthalmology & Visual Science*, 55(13), 2155-2155.
- Bowers, A. R., Keeney, K., & Peli, E. (2008). Community-based trial of a peripheral prism visual field expansion device for hemianopia. *Archives of ophthalmology*, 126(5), 657-664.
- Bowers, A. R., Keeney, K., & Peli, E. (2014). Randomized crossover clinical trial of real and sham peripheral prism glasses for hemianopia. *JAMA ophthalmology*, 132(2), 214-222.
- Chen, S. C., Suaning, G. J., Morley, J. W., & Lovell, N. H. (2009). Rehabilitation regimes based upon psychophysical studies of prosthetic vision. *Journal of neural engineering*, 6(3), 035009.
- Freeman, E. E., Munoz, B., Rubin, G., & West, S. K. (2007). Visual field loss increases the risk of falls in older adults: the Salisbury eye evaluation. *Investigative ophthalmology & visual science*, 48(10), 4445-4450.
- Giorgi, R. G., Woods, R. L., & Peli, E. (2009). Clinical and laboratory evaluation of peripheral prism glasses for hemianopia. *Optometry and vision science: official publication of the American Academy of Optometry*, 86(5), 492.

- Houston, K. E., Peli, E., Goldstein, R. B., & Bowers, A. R. (2018). Driving With Hemianopia VI: Peripheral Prisms and Perceptual-Motor Training Improve Detection in a Driving Simulator. *Translational vision science & technology*, 7(1), 5-5.
- Jung, J. H., & Peli, E. (2014). Impact of high power and angle of incidence on prism corrections for visual field loss. *Optical Engineering*, 53(6), 061707.
- Katz, M. (2004a). Visual acuity through Fresnel, refractive, and hybrid diffractive/refractive prisms. *Optometry-Journal of the American Optometric Association*, 75(8), 503-508.
- Katz, M. (2004b). Contrast sensitivity through hybrid diffractive, Fresnel, and refractive prisms. *Optometry-Journal of the American Optometric Association*, 75(8), 509-516.
- O'Neill, E. C., Connell, P. P., O'Connor, J. C., Brady, J., Reid, I., & Logan, P. (2011). Prism therapy and visual rehabilitation in homonymous visual field loss. *Optometry and vision science*, 88(2), 263-268.
- Papageorgiou, E., Hardiess, G., Schaeffel, F., Wiethoelter, H., Karnath, H. O., Mallot, H., ... & Schiefer, U. (2007). Assessment of vision-related quality of life in patients with homonymous visual field defects. *Graefe's Archive for Clinical and Experimental Ophthalmology*, 245(12), 1749-1758.
- Peli, E., & Jung, J. H. (2017). Multiplexing prisms for field expansion. *Optometry and vision science: official publication of the American Academy of Optometry*, 94(8), 817.
- Peli, E., Apfelbaum, H., Berson, E. L., & Goldstein, R. B. (2016a). The risk of pedestrian collisions with peripheral visual field loss. *Journal of vision*, 16(15), 5-5.
- Peli, E., Bowers, A. R., Keeney, K., & Jung, J. H. (2016b). High-power prismatic devices for oblique peripheral prisms. *Optometry and Vision Science*, 93(5), 521.
- Peli, E., Bowers, A. R., Keeney, K., & Jung, J. H. (2016c). High-power prismatic devices for oblique peripheral prisms. *Optometry and Vision Science*, 93(5), 521.
- Peli, E., Jung, J. H., Kurukuti, N. M., & Martin, F. V. (2018). High power multi-periscopic device for field expansion. *Investigative Ophthalmology & Visual Science*, 59(9), 638-638.
- Peli, E., Vargas-Martin, F., Kurukuti, N. M., & Jung, J. H. (2020). Multi-periscopic prism device for field expansion. *Biomedical optics express*, 11(9), 4872-4889. <https://doi.org/10.1364/BOE.399028>
- Yates, Joni & Lai, Sue & Duncan, Pamela & Studenski, Stephanie. (2002). Falls in community-dwelling stroke survivors: An accumulated impairments model. *Journal of rehabilitation research and development*. 39. 385-94.