Collision warning device for blind and visually impaired

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Clinical trial protocol and statistical analysis plan

Document date: 12 January 2021

Wearable Collision Warning Device for Blind and Visually Impaired: Clinical Trial

(As part of: 'Development of a Vision Assistive Device for Veterans with TBI-Associated Visual Dysfunctions')

Protocol Identifying Number: 2019P003610 (Formerly IRBnet #1007377)

Principal Investigator: Gang Luo and Alex Bowers

IND/IDE Sponsor: Not applicable

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LIST OF ABBREVIATIONS

DOD	Department of Defense
ETA	Electronic travel aid
HMD	Head mounted device
PPWS	Percentage preferred walking speed
USAMRMC	U.S. Army Medical Research and Materiel Command

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the DOD Terms of Award. The Principal Investigators will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

We agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigators: Gang Luo and Alex Bowers

Signed:

Date:

A signed statement of compliance has been uploaded as a separate document

PROTOCOL SUMMARY

Title: Wearable Collision Warning Device for Blind and Visually Impaired: Clinical Trial

Précis: A total of 42 participants with visual impairment or blindness will be trained to use a collision warning device that alerts them to impending collisions. They will use the device at home during their everyday mobililty for about 1 month with weekly calls from a researcher. The device will operate in two modes: active mode (intervention condition), when it gives warnings and, silent mode (control condition), when it does not give warnings. The device will be programmed to generate a different randomized active/silent schedule for each subject. Participants will not know whether it is in the active or silent mode. The number of collisions in the 2 device modes will be compared.

Objectives: Our overall objective is to establish a strong evidence base for the functional efficacy of our novel collision warning device. We hypothesize that the device will reduce the number of collision incidents experienced by visually-impaired and blind patients in their daily activities.

Specific aims (as detailed in the grant):

(1) Develop clinical study devices that have data recording functions, dispense the devices to patients for home use, and evaluate the efficacy of the device in the actual operational environment based on number of collision incidents.
(2) Characterize device reliability performance.
(3) Use questionnaires to record patients' perspectives on the utility and functionality of the device.

Secondary Objectives:

(1) Quantify nature and frequency of collision hazards in the operational environment.
(2) Assess potential of the device as a tool for future use in orientation and mobility training programs.

Endpoint Primary Endpoint: The primary outcome measure will be the difference in the number of collision incidents (defined as all contacts) in the active and silent modes. Fewer collision incidents during the active warning mode than the silent mode will indicate an effective intervention; the intervention benefit will be quantified by the percentage reduction in collision incidents.

Important Secondary Endpoints: Secondary outcomes will include (1) data on the number of body contacts in the active and silent modes and (2) data about participants' experiences with the device to guide future device development recorded using the device questionnaire administered at the

end of the study

Population:	42 participants with vision impairment or blindness who travel independently, age 18 and older in good health
Phase:	3
Number of Sites enrolling participants:	Schepens Eye Research Institute
Description of Study Agent :	Portable collision warning device for walking
Study Duration:	48 months (time from open to enrollment to completion of data analysis)
Participant Duration:	Varies dependent on device availability; period of home-use of device approximately 1 month

SCHEMATIC OF STUDY DESIGN

	Approximate timing*	**Tests to be administered**
Visit 1 at Schepens		Obtain informed consent Vision tests, cognitive status tests, mobility questionnaire
Visit 2 at Schepens		In-lab training in how to operate device
Visit 3 at Schepens	**Day 0**	Training with O&M Instructor and dispensing for home use
Follow-up 1 Phone	Day 7 (±3)	Check on progress with using the device
Follow-up 2 Phone	Day 14 (±3)	Check on progress with using the device
Follow-up 3 Phone	Day 21 (±3)	Check on progress with using the device
Visit 4 at Schepens	Day 28 (-7 to +14)	Device use questionnaire Return device

* Time windows are given in terms of business days (excluding weekends).

Timing starts at Visit 3 (Day 0) which is the visit at which the device is dispensed for home use. Normally the period of home use will be about one month. Therefore Visit 4 is at Day 28. However, if participants are very active travelers and the device records a lot of data very quickly, then the period of home use might be less than one month and Visit 4 might be before Day 28. In some cases, Visit 4 might be after Day 28, in particular if the subject has limited availability to attend Schepens; therefore, for the final visit, a 2-week period has been allowed after Day 28.

The period between Visit 1 and Visit 3 may vary widely dependent on device and subject availability from as little as 0 days (screening done on same day as training for a subject from outside of the New England area) to as long as one year.

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

This clinical trial evaluates a novel collision warning device invented by Dr. Luo and colleagues. The device provides tactile warnings of potential collisions.

Prior studies of the collision warning device

A prototype of the portable collision warning device was previously evaluated in a lab-based clinical study in which participants were given brief training in how to use the device and then walked through an indoor obstacle course (in a large room) both with and without the device. The course included a high density of soft obstacles that would not cause any injury if a participant made contact with them

(including inflatable plastic trees and paper objects hanging from the ceiling). Participants included 13 subjects with tunnel vision (peripheral field loss) and 12 subjects with hemianopia (loss of half the field of vision in both eyes). The number of contacts with the obstacles was significantly lower when using the device than when walking through the course without the device (Pundlik, Tomasi and Luo, 2014). There were no adverse events. These results demonstrate preliminary efficacy and safety of the device within a controlled environment.

Pilot study to be conducted before the clinical trial

The prior study only evaluated the collision device within the indoor setting of our lab. Therefore, before starting the clinical trial, we will conduct a small pilot study of the device in which people with peripheral field loss or blindness/severe vision loss will take the device home and use it in their everyday mobility (as we plan to do for the clinical trial). The protocol for this pilot study has already been approved by the local IRB at Massachusetts Eye and Ear and also by the Department of Defense. Recruitment for the pilot study has started. The pilot study will provide data on the safety and potential efficacy of the device in everyday use in an uncontrolled environment. Data from the pilot study will be used to finalize the design of the clinical trial and verify the sample size calculation.

Prior studies of other electronic travel aids

Prior clinical trials of electronic travel aids (ETAs) aimed at improving obstacle detection/collision avoidance typically involved a relatively small sample of visually-impaired participants (n = 1 to 20) or blindfolded normally-sighted participants. Performance with the ETA was compared to performance without the ETA and/or to performance with another device, often evaluated after only a short period of familiarization and training with no opportunity to use the device during habitual mobility (Roentgen, Gelderblom, Soede, & de Witte, 2009; Roentgen, Gelderblom, & de Witte, 2012; Vincent et al., 2013). The evaluation tools were mostly questionnaires (addressing device functionality and user satisfaction) and/or mobility assessments (walking speed and number of contacts/mobility errors) on relatively short indoor or outdoor courses usually conducted in a laboratory or rehabilitation setting (U. Roentgen, et al., 2009). Only one study (Darling, Goodrich, & Wiley, 1977) included observation and assessment by orientation and mobility instructors in the participant's home and work place.

Prior clinical trials of visual aids that enhance vision to assist with obstacle detection/collision avoidance have included optical and HMD-based devices to expand the visual field of patients with hemianopia (Bowers, Keeney, & Peli, 2008; Lee & Perez, 1999; O'Neill et al., 2011) and tunnel vision (Bowers, Luo, Rensing, & Peli, 2004), and HMD devices to assist patients with night blindness (Hartong, Jorritsma, Neve, Melis-Dankers, & Kooijman, 2004; Hartong & Kooijman, 2006). As with the ETA studies, they typically involved small sample sizes (n = 6 to 40), compared performance with the device to performance without the device or performance with another device, and used questionnaires and mobility courses as assessment tools. While questionnaires are essential in evaluating the user's perspective, they do not provide a direct measure of mobility performance with the device. Indoor and outdoor mobility courses do provide a direct measure of performance in controlled environmental conditions, but they may fail to capture what happens in everyday mobility and usually depend on observer-based ratings of performance.

Clinical trial of novel collision warning device

Our proposed trial design addresses many of the limitations of prior studies of other electronic travel aids, and most importantly, evaluates the extent to which the collision warning device reduces collisions in everyday mobility.

2.2 RATIONALE

While body armor that protects vital organs and the skull is saving soldiers' lives, their eyes and brain remain particularly vulnerable to explosions. The DOD has confirmed that about 13 percent of all wounded evacuees from Iraq have experienced a serious eye injury (Thach et al., 2008), which often results in severe vision loss or even complete blindness. This is the highest percentage for any war in American history. Besides direct ocular injuries, traumatic brain injuries (TBI) also cause a variety of vision problems. Moderate to severe TBI may result in loss of visual field, including hemianopia (the loss of half the visual field) and tunnel vision (concentric loss of peripheral visual field). In a recent report about TBI patients at the Palo Alto Polytrauma Rehabilitation Center (service-members injured in OIF and OEF), about one-third of the veterans with TBI had visual field loss (Brahm et al., 2009). Furthermore, we also have to consider the thousands of older veterans who have significant visual field loss as a result of a stroke, non-military traumatic brain injury, or age-related ocular disease such as advanced glaucoma. Approximately 80,000 veterans are stroke survivors (Kwon et al., 2006), of which 30 to 50% have visual field loss (Rowe et al., 2009; Townend et al., 2007).

Both blindness and visual field loss compromise a person’s ability to move about safely and independently with adverse effects on independence, quality of life and employment opportunities. In particular, detection of potential hazards in the environment is impaired (Bowers, Mandel, Goldstein, & Peli, 2009; Friedman, Freeman, Munoz, Jampel, & West, 2007; Turano, Geruschat, Stahl, & Massof, 1999) which puts visually-impaired and blind people at a high risk for collisions. Indeed, a large number of studies have shown that visual impairment, especially visual field loss, substantially increases the risk of falls and injuries (Coleman et al., 2007; Freeman, Munoz, Rubin, & West, 2007; Haymes, LeBlanc, Nicolela, Chiasson, & Chauhan, 2007; Legood, Scuffham, & Cryer, 2002). In terms of the cost of collision-related injuries, people with any degree of visual impairment have about 47% higher costs than the normally sighted, while the costs for patients with moderate to severe vision loss are the same as those for people with complete blindness (Bramley, Peeples, Walt, Juhasz, & Hansen, 2008). As therapeutic vision restoration solutions for severe eye or brain injuries are not yet available, rehabilitation approaches through assistive technologies and training are sometimes the only solutions for mitigating vision-related problems.

We hypothesize that the novel collision warning device tested in this study will reduce the number of collisions of veterans and civilians with blindness or vision impairment resulting from eye and brain injuries. Ultimately, our goal is to develop the device in the form of a low-cost, smart-phone app. The 2 device modes, active and silent, will permit analysis of device effectiveness and pose minimal risk to

users. The device is not intended to replace habitual mobility aids such as a long cane and participants will be encouraged to use the device in conjunction with their habitual mobility aids.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The collision warning device provides tactile warnings to alert participants to potential obstacles. People with visual impairments or blindness have an increased risk of collisions and accidents compared to people with a full field of vision. We believe that this risk will be reduced with the collision warning device. The risk when using the device is no greater than would normally be encountered in everyday mobility situations. Participants will be clearly told that they should not rely on the device, should continue to be vigilant at all times and should continue to use their habitual mobility devices (telescopes, long cane etc.). The indoor obstacle course contains light, soft, and movable objects presenting minimal risk of falls or injury. Experimenters will follow participants to ensure their safety and intervene if necessary.

The value of the information to be gained about the device and the nature of collision incidents experienced by people with blindness and vision impairment far outweigh the minimal risks involved in study participation.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants will not be permitted to keep the device at the end of the study. Nevertheless, they may benefit from the training provided when learning to use the device.

3 OBJECTIVES AND PURPOSE

Our overall objective is to establish a strong evidence base for the functional efficacy of our novel collision warning device. We hypothesize that the device will reduce the number of collision incidents experienced by visually-impaired and blind patients in their daily activities.

Specific aims (as detailed in the grant):

(1) Develop clinical study devices that have data recording functions, dispense the devices to patients for home use, and evaluate the efficacy of the device in the actual operational environment based on number of collision incidents.
(2) Characterize device reliability performance.
(3) Use questionnaires to record patients' perspectives on the utility and functionality of the device.

Secondary Objective(s)

(1) Quantify nature and frequency of collision hazards in the operational environment.
(2) Assess potential of the device as a tool for future use in orientation and mobility training programs.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This phase 3 clinical trial will use a prospective, double-masked, controlled within-subjects design in which the number of collision incidents in the active mode (the intervention condition) will be compared to the number of collision incidents in the silent mode (the control condition). A within subjects design has been selected for two main reasons: firstly, to control between-participant variability, found to be high in our previous studies with visually-impaired patients (Bowers, et al., 2004; Bowers, et al., 2009; Luo & Peli, 2006; Luo, Satgunam, & Peli, 2012); and secondly, to minimize the number of participants that will be required in order to achieve sufficient statistical power such that recruitment and data collection can realistically be completed within the time span of the grant.

Subject participation will be between 1 and 12 months (depending on device availability and subject availability for the home-use part of the trial), with participants using the device at home for about 1 month. At the first visit, vision measures, cognitive status measures and the Independent Mobility Questionnaire will be administered. The second and third visits will be training sessions during which participants will be instructed in how to use the collision warning device. Participants who demonstrate that they can use the device correctly will then be permitted to take it home. An orientation and mobility specialist will make the determination about whether each participant can take the device home.

Participants will be asked to use the device as much as possible for about 1 month when moving about indoors and outdoors so that all potential collisions will be recorded. Participants will be instructed to continue to use their habitual visual aids or mobility aids during the 1-month period. Each week while using the collision warning device, participants will be contacted by phone to check on their progress with the device. After about one month of using the device, participants will return to Schepens for the final visit at which they will complete a questionnaire addressing their experiences of using the device.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary outcome measure will be the difference in the number of collision incidents (all contacts) in the active and silent modes. Fewer collision incidents during the active warning mode than the silent mode will indicate an effective intervention; the intervention benefit will be quantified by the percentage reduction in collision incidents (all contacts).

4.2.2 SECONDARY ENDPOINTS

Secondary outcomes will include:

1) Data on the number of body contacts in the active and silent modes.
2) Additional data about participants' experiences with the device to guide future device development, recorded using the device questionnaire administered at the end of the study.

4.2.3 EXPLORATORY ENDPOINTS

In addition to the primary and secondary outcome measures for the clinical trial, the collision warning device will collect a wealth of information about collision incidents. When imminent collisions are detected, video will be saved for each warning given by the device. These images will provide details about the nature and circumstances of near collisions and actual collisions of participants. These data will be valuable for increasing our knowledge about collision incidents of blind and visually impaired people in everyday mobility and will help guide the development of future mobility devices and training programs. Our O&M consultant will also review images from some typical cases to assess whether, in the future, a collision detection device with recording capabilities would be helpful in O&M training; in particular, for providing remote (long distance) training for clients in rural areas (e.g., the clients could send the images to the O&M instructor to review and provide feedback).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

In order to participate in this study, an individual must meet the following inclusion criteria:

- Provision of signed and dated informed consent form
- Blindness (or very limited vision with visual acuity no better than “counting fingers”), or tunnel vision (≤ 40° remaining visual field) with visual acuity of at least 20/200;
- Able to walk independently either with or without mobility aids such as a long cane or guide dog (but without the aid of a sighted guide);
- Reports at least minor bumps or collisions within the last 3 months;
- Male or female, at least 18 years of age.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following will be excluded from participation in this study:

- Currently participating in a mobility training program;
- Diagnosed dementia;
- Significant cognitive decline (more than 4 errors on the Short Portable Mental Status Questionnaire)

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants with vision impairment (severe vision loss, hemianopia, tunnel vision) will be recruited from the following sources:

(1) Referrals from orientation and mobility specialists who provide services for visually impaired and blind people in the Greater Boston area, including orientation and mobility specialists from the Carroll Center for the Blind and the Massachusetts Commission for the Blind;

(2) Referrals from practitioners at vision rehabilitation and neuro-ophthalmology clinics in the Greater Boston Area;

For recruitment from sources (1) and (2), a recruitment pack will be distributed to orientation and mobility specialists at the Massachusetts Commission for the Blind, the Carroll Center for the Blind

and practitioners in the Boston area. This pack includes an information letter for the practitioner/mobility specialist, an information sheet about the study for the patient and a HIPAA form for disclosure of contact information, diagnosis and vision status for research purposes. Potential participants can either complete the disclosure form which will be returned to Schepens by the service provider, or the patient can contact the study coordinator directly by phone. The recruitment coordinator will call patients who complete the disclosure form and give them further information about the study, and will schedule a screening visit if the person is interested in participating (see Telephone script).

3) Local advertisements/flyers with study information, posted on listservs and other online information networks for the blind and visually impaired, and sent out through newsletters of groups for the visually impaired and blind, such as the Bay State Council of the Blind, Massachusetts Association of the Blind, the Visually Impaired and Blind User Group, and the Talking Information Center. Participants with vision loss who learn about the study through advertisements and local flyers will contact the study coordinator directly to express interest. (Contact information will be provided on the advertisement).

4) Prior volunteers who have previously participated in studies in our lab and who have given their consent to be contacted about future studies. Participants identified through our pool of volunteers will be contacted directly by phone by the recruitment coordinator.

Participants who are interested in participating will be invited to Schepens for an initial study visit. After the informed consent procedure, vision measures will be taken to determine eligibility for the study.

An experimenter will be checking in with subjects approximately once every week during the study to check on their progress with the device. At this time they will also confirm that the participant wants to continue participation.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may terminate participation in the study if:

- A participant is not using the device correctly or appears to be engaging in risky behaviors when using the device.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Any other situation occurs such that continued participation in the study would not be in the best interest of the participant

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

If a participant withdraws or is terminated from the study, they will be asked to return the device and, if willing, complete a questionnaire about their experience with the device.

Our sample size estimate includes an allowance for withdrawal/attrition. If more participants withdraw than anticipated, additional participants will be recruited to ensure we reach our target enrollment to complete the clinical trial.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and funding agency. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

The device is developed and assembled by researchers in our lab. It will be checked by MEEI engineering prior to dispensing to participants to ensure safety.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A - The collision warning device has never been marketed and is assembled in our lab.

6.1.3 PRODUCT STORAGE AND STABILITY

Devices will be kept in experimenters' locked offices prior to dispensing to participants. At the last study visit, after each participant completes the study, the device will be taken back and retained in a locked office and made ready for dispensing to another subject. The device will not be destroyed after use.

6.1.4 PREPARATION

Each of the devices that will be used for the clinical trial will be checked by the engineering department at Massachusetts Eye and Ear Infirmary to ensure safety before they are used by participants. An orientation and mobility specialist will ensure that participants can operate and use the device safely before they are permitted to take it home.

6.1.5 DOSING AND ADMINISTRATION

N/A

6.1.6 ROUTE OF ADMINISTRATION

N/A

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

N/A

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

N/A

6.1.9 DURATION OF THERAPY

N/A

6.1.10 TRACKING OF DOSE

N/A

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

The portable collision warning device is exempt as a Class 1 ophthalmic device. The device is a pocket-sized, electronic system (see Figure 1) that primarily includes a micro-computer, a miniature camera (120° horizontal and 60° vertical field of view), a SD card (that can record more than 400 hours of data), a gyro-sensor, an accelerometer, and a rechargeable battery. The device also comes with a pair of Bluetooth vibrating bracelets with their own charger. The overall dimensions of the current prototype device are 5.1 x 2.5 x 1.0 inches, and it weighs 7.4 ounces. The processing unit is contained within a single-strap backpack, with the camera internally placed in the shoulder strap, so the device will be camouflaged and cosmetically acceptable for daily use (Figure 1). The overall weight of the device along with the backpack is ≈ 1.8lbs. The camera will be connected to the processing unit and worn facing outwards. Slight movement of the camera will not be a problem. (A camera tightly attached to body will bounce as the user walks anyway.) The image processing algorithm in our device can compensate for camera movements when walking using signals from the gyro-sensor.

When a potential collision incident is detected, the device will cause the wristbands to vibrate. Wearing a pair of wristbands, one on each wrist, the subjects will be able to receive directional information from our device about the impending collision. When potential collisions are on one side, the bracelet on the same side will vibrate. When potential collisions are in the forward direction, both bracelets will vibrate. The vibrations will begin when the user is approximately 3 seconds away from the collision risk (assuming current trajectories are maintained) and continue for as long as the collision risk is ongoing. The device is designed to only give warnings about high risk collisions, so the users will not be continually bombarded by warnings for every potential collision object in the environment. Furthermore, the thresholds can be individualized for each user.

Operation of the device will be straightforward. The controls will be designed to be easy for visually impaired or blind people to use. The device will be turned on by sliding the power switch to the on position and turned off by sliding it back to the off position. A plug-in charger will be provided for charging the battery. After the battery is fully charged, the device will run continuously for at least 6 hours. However, the actual period for which the device will operate will be longer than 6 hours as the device will switch to low power mode to save the battery when no walking of the participant is detected by the motion sensors within one minute. Once movement is detected, the device will turn on automatically. Depending on a person's activity level, the device may be able to function for several days without being charged. Wristbands will need to be charged separately from the device using their own charger. The wristband units hold the charge for about 5-6 days.

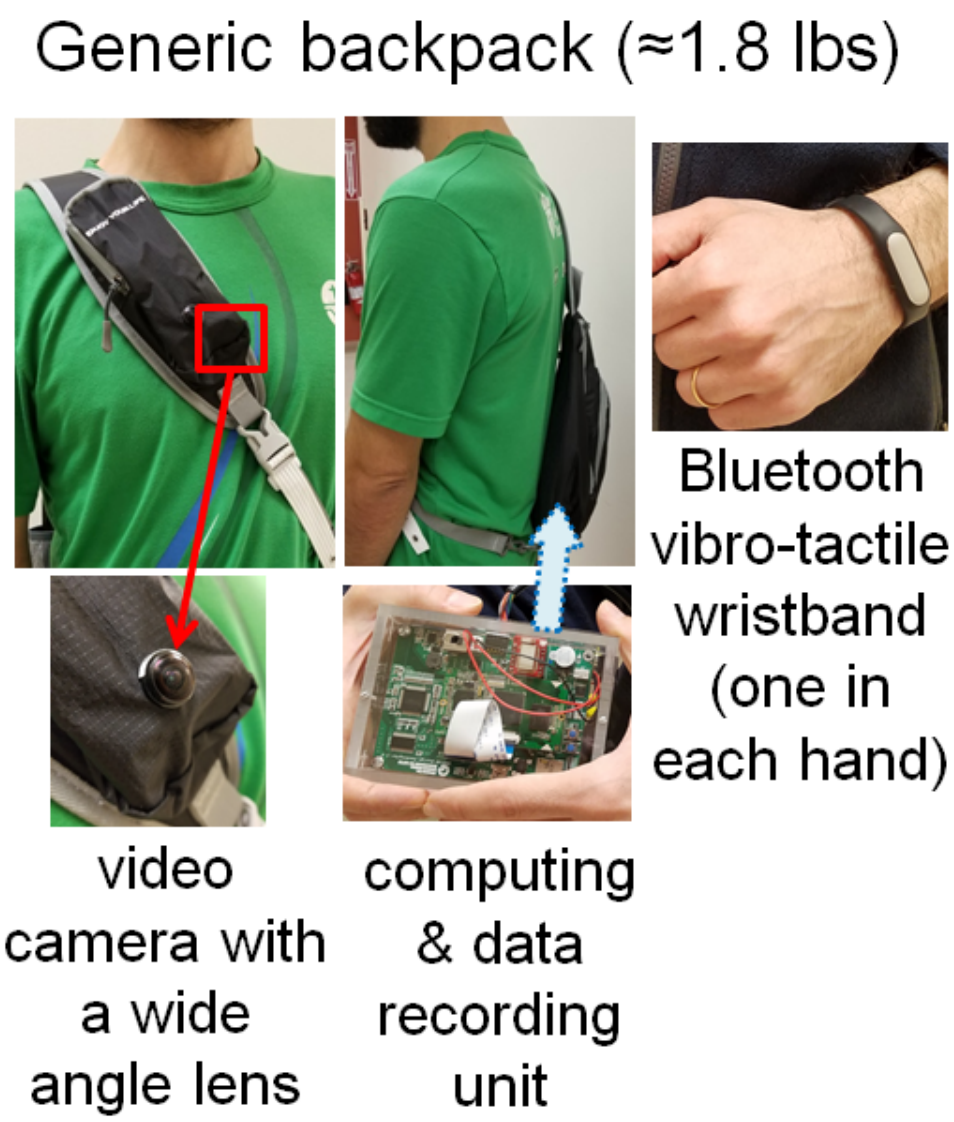

Figure 1. The entire collision warning device is contained in a backpack. It consists of two main parts connected by a wire. The main processing board (computing and data recording unit) is in the backpack. The camera is worn at chest level. The camera module also includes miniaturized motion sensors. The device can issue coded collision warnings via two Bluetooth vibro-tactile wristbands (one for each hand).

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The device will be given to a participant by a member of the research team when the participant attends the training visit. The device will be returned by the participant to a member of the research team when the participant comes for the final study visit. A device accountability log of date in and out will be maintained by study staff. If for some reason the participant is unable to attend for the final visit, arrangements will be made by study staff for the participant to return the device by a courier service (e.g., FedEx) or a member of the research team will go to the participant's home to collect the device.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Visit 1 at Schepens
Screening procedures will be performed at the first study visit to determine eligibility for the study. Informed consent will be obtained prior to starting the battery of screening tests.

The following non-invasive tests will be performed at Visit 1:

- Visual acuity
- Visual fields
- Short Portable Mental Status Questionnaire (this is a short test of mental status which can be read out loud to participants and is therefore suitable for administration to blind or severely visually impaired participants).
- Short screening questionnaire (brief questions about diagnosis, visual status, mobility and devices used)
- Independent mobility questionnaire (Turano et al. 1999) asking about difficulty with mobility and bumping into objects, including some additional questions about walking habits.
- For hemianopic subjects only: standard clinical tests of spatial neglect including the Schenkenberg line bisection test and the Gauthier bells test

As only 4 devices will be used in the clinical trial, participants who are determined to be eligible for the study will be placed on a waiting list until it is known when a device will be available for them to use. They will then be contacted to arrange subsequent visits.

Visit 2 at Schepens
The second visit will be a training session during which participants will be given basic instructions in the lab in how to operate the collision warning device (how to operate the device, how to use the wristbands, how to charge the batteries etc.).

Visit 3 at Schepens
At visit 3, participants will receive more comprehensive training with an Orientation and Mobility specialist including walking along short indoor and outdoor routes. Those who demonstrate that they can use the device correctly will then be permitted to take it home. They will be asked to use the device as much as possible for approximately 1 month when moving about indoors and outdoors so that all potential collisions will be recorded. They will be instructed to continue to use their habitual visual aids or mobility aids during the 1-month period.

Telephone follow ups
Each week of using the collision warning device, participants will be contacted by phone to check on their progress with the device.

Visit 4 at Schepens
After approximately one month of using the device, participants will return to Schepens for the final visit at which they will complete a device questionnaire addressing their experiences of using the device. The device questionnaire will include questions addressing satisfaction with the device, usability of the device, functionality of the device, ergonomic aspects of the device, the impact on their lives, and

suggestions for future improvements. Questions will be based on those in the QUEST questionnaire (Quebec User Evaluation of Satisfaction with Assistive Technology) (Demers et al., 2002) as well as questionnaires we devised for prior evaluations of mobility devices for people with visual field loss (Bowers et al., 2008; Bowers et al., 2004).

For participants who are unable to attend the final visit, alternative arrangements may be made. Either a member of the research team will go to the participant's home to collect the device or arrangements will be made by study staff for the participant to return the device by a courier service. In such cases the device questionnaire may be administered by telephone interview.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

N/A

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

N/A

7.2.2 OTHER ASSAYS OR PROCEDURES

N/A

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

N/A

7.2.4 SPECIMEN SHIPMENT

N/A

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Visit 1– Screening

- Obtain informed consent of potential participant verified by signature on study informed consent form.

Consent will be obtained before starting the screening tests (there is only one consent form for the clinical trial which includes screening tests):

- Visual acuity (logMAR Snellen chart or Berkeley Rudimentary Vision Test)
- Contrast sensitivity (Mars chart)
- Visual fields
- Short Portable Mental Status Questionnaire (this is a short test of mental status which can be read out loud to participants and is therefore suitable for administration to blind or severely visually impaired participants).

- Short screening questionnaire (brief questions about diagnosis, visual status, mobility and devices used)
- For hemianopic subjects only: standard clinical tests of spatial neglect including the Schenkenberg line bisection test and the Gauthier bells test

7.3.2 ENROLLMENT/BASELINE/TRAINING

Visit 1– Baseline data

Baseline data will be collected at visit 1 for participants that meet the study criteria:

- Obtain demographic information.
- Administer independent mobility questionnaire (Turano et al. 1999)

Visit 2 – Initial Training

- Acclimate participant with the device
- Train participant in how to operate the device (turn on/off, charge batteries, use wristbands etc)

Visit 3– Training and dispense device (Day 0)

- Train participant in how to use the device when walking short indoor and outdoor routes
- Determine whether participant can use device correctly and safely
- Dispense device to participant for approximately 1months of home use
- Provide instructions on how to use device

7.3.3 FOLLOW-UP

Telephone follow ups (Weekly)

Each week after dispensing the device for home use, a researcher will contact the participant by phone to check on their progress with the device

- Record adverse events as reported by participant
- Record participants feedback about using the device and provide further instructions if necessary

7.3.4 FINAL STUDY VISIT

Final study visit (Day 28)

- Administer device questionnaires at final visit
- Record adverse events as reported by participant or observed by investigator
- Retain device

7.3.5 EARLY TERMINATION VISIT

An experimenter will be checking in with subjects approximately once every week when they are using the device at home to check on their progress with the device. Any subject that is not using the device correctly or appears to be engaging in risky behaviors when using the device will be terminated early. If at any point subjects experience difficulty and wish to withdraw from the study they can notify the experimenter and discontinue participation. They will be asked to return the device and, if willing, complete a questionnaire about their experience with the device.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Screening and baseline (visit 1)	Training (Visit 2)	Training (visit 2)	Telephone Follow up	Telepone Followe Up	Telephone follow up	Telephone Follow Up	Final visit (visit 4)							
Informed consent	X														
Demographics	X														
Visual acuity	X														
Visual fields	X														
Brief screening questionnaire	X														
Independent mobility questionnaire	X														
Short portable mental status	X														
For hemianopic subjects: spatial neglect tests	X														
Training to use the device		X	X												
Dispense device with instructions			X												
Check on use of device				X	X	X	X								
Adverse event evaluation				X	X	X	X	X							
Device questionnaire								X							
Retain device								X							

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

No sensitive procedures will be administered.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

N/A

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Participants will not be permitted to keep the device when they complete the study. They will have to return the device at the final visit.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any event temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death
- Is life threatening
- Requires hospitalization/prolongation of hospitalization
- Results in persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

- It is unexpected (in terms of nature, severity, 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)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The following guidelines will be used to describe adverse event severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

For example if a subject has a minor collision with an object while walking when using the device which results in a little bruising or a minor cut, the event would be classified as mild.

8.2.2 RELATIONSHIP TO STUDY AGENT

The PI's assessment of an AE's relationship to the study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether an incident or observation is an AE, the event will be reported. 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.

8.2.3 EXPECTEDNESS

Dr. Bowers and Dr. Luo (co-PIs) 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.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Study personnel will ask about AEs during the telephone follow ups and the final study visit at Schepens. These will be collected as solicited events.

In addition, participants will be instructed to contact study personnel between visits if an AE occurs. If a participant contacts a member of the study team to report an event between scheduled visits, the event will be collected as an unsolicited event. Double capture of events (captured both as an unsolicited and a solicited AE) will be avoided by asking the participant whether the event has already been reported (at a previous visit or between visits)

Information to be collected about each event includes event description, time of onset, study personnel's assessment of severity, relationship to study device(assessed only by PI), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent will require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, an investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All adverse events whether serious or non-serious, expected or unexpected, will be reported as soon as possible to the PIs (by a subject or member of the research team). The PIs will review the details of each event to determine the severity, whether expected or unexpected, and decide what further reporting is required.

Serious adverse events and unanticipated problems
These events will be reported immediately to the PIs (within a few hours). Please see sections 8.4.2 and 8.4.3 below for details.

Non-serious, expected adverse events
All non-serious expected adverse events will be logged by a member of the research team at the time they are reported and will be reviewed by the PIs within 7 days of the event occurring. A summary of all non-serious expected adverse events will be provided to the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office on an annual basis, as part of the annual IRB review of the protocol.

Non-serious, unexpected adverse events
Unexpected, non-serious adverse events will be logged by a member of the research team at the time they are reported and will be reviewed by the PIs within 7 days of the event occurring. These events will

be reported to the local IRB within 30 calendar days from the time the PI became aware of the event. A summary of all non-serious unexpected adverse events will be provided to the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office on an annual basis, as part of the annual IRB review of the protocol.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Study personnel will report all serious adverse events (expected or unexpected, related or unrelated) immediately to the PIs. Subjects may also submit a report directly to the Research Administration (contact details are on the consent form), in which case the IRB Chair is notified immediately.

The PIs will notify the local IRB, the Safety Monitor and the study sponsor (see below) within 72 hours of becoming aware of the event.

All deaths and immediately life-threatening events, whether related or unrelated, will be reported by the PIs to the local IRB, the Safety Monitor and the study sponsor (see below) within 24 hours of the PI's knowledge of the event.

After initial notification, a written report will be submitted to the IRB, the Safety Monitor and the study sponsor within 7 calendar days of initial notification.

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the adherence to be stable.

Reporting to study sponsor
All serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR¬ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Study personnel will report all incidents or events that meet the criteria for unanticipated problems immediately to the PIs. The PIs will then report the unanticipated problem to the local IRB, the Safety Monitor and the study sponsor (see below).

Unanticipated problems that are serious adverse events will be reported to the IRB and to the study sponsor within 72 hours of the PIs becoming aware of the event.

If the unanticipated problem results in a subject's death or is life-threatening, it will be reported by the PIs to the local IRB and the study sponsor (see below) within 24 hours of the PI's knowledge of the event.

After initial notification, a written report will be submitted to the IRB, the Safety Monitor and the study sponsor within 7 calendar days of initial notification. In addition to a description of the event, the report

will include an explanation of the basis for determining that the event represents an unanticipated problem and a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

Any other anticipated problems that do not involve risks to subjects or others will be reported to the IRB and to the study sponsor on an annual basis, as part of the annual IRB review of the protocol.

Reporting to study sponsor

All unanticipated problems involving risk to subjects or others will be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR¬ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

8.4.4 EVENTS OF SPECIAL INTEREST

N/A

8.4.5 REPORTING OF PREGNANCY

N/A

8.5 STUDY HALTING RULES

Administration of the study device will be halted immediately if there is a serious adverse event or a serious unanticipated problem. The PIs will notify the local IRB, the Safety Monitor and the study sponsor within 24 hours.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an independent Research Safety Monitor (Dr. Russell Woods). Dr. Woods is totally independent from the study, does not have any conflicts of interest, and has expertise relevant to the duties he will perform as the Research Safety Monitor (see biosketch uploaded in IRBnet). The study team will send reports to the Safety Monitor addressing recruitment, withdrawals, adverse event reports and interim analyses (when performed). The Safety Monitor will provide an annual report to the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office as part of the annual IRB review of the protocol. If there are any urgent concerns, the Safety Monitor will immediately contact the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office. The Safety Monitor will have authority to stop the research protocol in progress, remove individual human subjects from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the local IRB can assess his report.

9 CLINICAL MONITORING

Monitoring will be conducted by the PIs to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Please also see section 12.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

There will not be a formal SAP.

10.2 STATISTICAL HYPOTHESES

Primary efficacy endpoint

The primary outcome measure will be the number of collision incidents (all contacts) in the active and silent modes. Fewer collision incidents during the active warning mode than the silent mode will indicate an effective intervention. This analysis will include data collected throughout all of the period of home-use of the device.

Since subjects will likely use the device for differing amounts of time and are exposed to different number of hazards, the number of collisions will be expressed as the rate of collisions for analyses.

Null hypothesis: There will be no difference in the rate of collisions between the active and silent modes

Alternative hypothesis: There will be a difference in the rate of collisions between the active and silent modes

10.3 ANALYSIS DATASETS

The dataset for the analysis of the primary efficacy outcome measure will be a modified intention-to-treat dataset. Only participants who have completed the home-use part of the study will be included in the analysis.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This phase 3 clinical trial will use a prospective, double-masked, controlled within-subjects design. Descriptive statistics for continuous data for each of the primary and secondary endpoints will be presented as means with standard deviations or medians and ranges, as appropriate. The normality of the data will be examined and appropriate statistics and descriptives used based on the results. For inferential statistics, an alpha level of 0.05 will be taken to indicate statistical significance with correction for multiple comparisons when necessary.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The analysis will start with descriptive and graphical summaries of the rate of collision incidents (all contacts) in the active and silent modes, and the difference between active and silent modes. The rate will be computed as the rate of contacts per 100 true hazards (reviewed) per hour. The rate computation takes account of both duration of use and number of true hazards encountered, since some subjects might walk for longer but encounter fewer hazards while others might encounter more hazards in a shorter duration. Contacts will include all contacts with the collision hazard, either with their mobility aids (such as long cane) or body (touching with hand, bumping into the obstacle).

The primary analysis will start by comparing the within-subject difference in the rate of collisions (all contacts) between the active and silent modes using a Wilcoxon Signed-Rank test.

Next a model will be constructed to evaluate within-subject differences in the rates of collisions taking account of other factors that might affect the primary outcome measure. Since the number of contacts will represent overinflated count data, negative binomial regression models – considered to be more appropriate than Poisson regression models for such distributions – will be used for evaluating the association between rate of contacts and device operating condition (active vs. silent). In actual implementation of the regression model, the outcome will be set as the number of contacts (all contacts), while the exposure variable consisting of the duration of device use and the number of true hazards will be the offsets, and the estimated regression coefficients will be expressed as the rate ratio (β). The role of other possible predictors that could potentially affect the rate of contacts will be analyzed. These predictors will be taken from four broad categories: device data, demographics, vision characteristics, and mobility characteristics. Each predictor will be evaluated individually in a generalized mixed effects modeling framework (because we want to estimate within-subject effects) that will also include device condition. Any significant predictors ($p < 0.05$) and possible confounders (causing $\geqslant$ 10% change in the rate ratio for the device condition predictor) will be selected for inclusion in the final model to determine the effect of device condition on rate of contacts.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of the secondary measure, number of body contacts will follow that same methods as described for the primary measure, number of collisions (all contacts). Number of body contacts will be expressed as the rate of body contacts per 100 true hazards per hour.

Rating scale responses from the device questionnaire will be summarized using descriptive statistics. Responses to open-ended questions will be examined for common themes and coded accordingly.

10.4.4 SAFETY ANALYSES

Our main measure of safety is the number and severity of collision incidents when using the device in everyday mobility. However, this is also our main measure of device efficacy. If the number and severity of collision incidents is reduced when the device is in active mode compared to the silent mode, this would suggest that the device is effective. However, if the number and severity of collisions is greater when the device is in the active than the silent mode, then this would suggest that the device is not

effective and the device warnings were in some way causing collisions (rather than helping to avoid collisions). Collision incidents will be summarized with descriptive statistics. Incidents will be classified in terms of severity using the scale described in section 8.2.1.

If a severe or serious adverse event occurs before the code for the silent/active mode is broken, a non-masked member of the study team will review the data recorded by the device to examine the events leading to the collision and will determine whether the collision occurred when the device was in the active or the silent mode.

Please also see section 8.

10.4.5 ADHERENCE AND RETENTION ANALYSES

The amount that the collision warning device is used each day will be recorded by the device and will be summarized with descriptive statistics. The number of participants who withdraw from the study after visit 1, after visit 2, and after starting to use the device at home will be recorded and summarized with descriptive statistics.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will be used to describe subjects included in analyses in regards to age, gender, and mobility.

10.4.7 PLANNED INTERIM ANALYSES

10.4.7.1 SAFETY REVIEW

Please see sections 5.5, 8.5 and 8.6

Adverse events will be monitored on an ongoing basis throughout the study. Administration of the study device will be halted immediately if there is a serious adverse event or a serious unanticipated problem. There are no statistical rules to halt enrollment.

10.4.7.2 EFFICACY REVIEW

An informal interim analysis will be conducted after about one-half of the subjects have completed the study. One of the masked study team members will conduct the analysis. The results of the analysis will be reported to the Safety Monitor and also to the Department of Defense, in a quarterly or annual report.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Please see section 10.4.2 (analysis of primary efficacy endpoint).

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Correction for multiple comparisons will be used when appropriate.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

It is very unlikely that we will list individual data by measure and time point. If individual data are listed, the data will be totally de-identified.

10.4.11 EXPLORATORY ANALYSES

Data about collisions incidents during the period of using the device at home will be examined and a method of categorizing the incidents will be developed. For example, considering factors such as the location of the incident (e.g., indoors or outdoors), whether the collision object was stationary or moving, and the nature of the object (pedestrian, wall, overhang, etc.). The effect of factors such as level of vision loss, age, gender, activity level and walking speed will also be examined.

10.5 SAMPLE SIZE

Justification for our sample size estimate is provided by the results of the prior obstacle-course study with the first prototype device (Shrinivas, Tomasi and Luo, 2014). Although collision incidents on the course were much higher than in real-world mobility, the results nevertheless demonstrate our ability to measure significant device effects with a cohort of only 24 participants. Specifically, in the 13 tunnel vision patients in that study, an average effect size of 0.4 related to walking with the device was observed (pairwise difference between the conditions), with 0.38 as the standard deviation of change. Assuming that the effect size is halved (0.2) to account for real-world mobility, the standard deviation of change remains the same, alpha = 0.05, and power of 0.8, we get a sample size of 31. With a 30% attrition rate (assuming multi visit study may have higher attrition), we arrive at the final sample size of 42.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

The device will be programmed to generate a different randomized active/silent schedule for each subject. Both the subjects and the investigators conducting statistical analyses will be masked as to when the device is in active/silent mode.

Data logged by the device during each mode will be coded either as mode A or B. The computer-generated coding for the active/silent modes for each subject will be saved as a computer file and stored in a secure location by a research team member who is not involved in data analyses.

Subjects will be masked in that they will not be informed when the device is in the silent or active mode. They will be told that the device may sometimes go into silent mode and not give any warning messages. They will be advised that they will not know when it is in silent mode and that they should be always vigilant about collision hazards.

The code for silent/active mode will not be broken until after the final data analyses are completed.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

We have no plans to evaluate the success of masking.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

The code for silent/active mode will not be broken until after the final data analyses are completed.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PIs and study team will maintain appropriate research records for this clinical trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. These records will include hard-copy record forms and electronic data from the collision warning device.

Schepens will provide direct access to source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with all the data entered on hard copy record sheets and then entered into the electronic study spreadsheet (database). The records and data entries will be monitored on an ongoing basis by a second researcher, not responsible for original data entry. In prior studies we have found this to be a very effective method of ensuring data quality.

The PIs will be responsible for addressing quality assurance issues (such as correcting procedures that are not in compliance with the protocol) while the study coordinator will be responsible for correcting data entry errors.

Schepens will provide direct access to source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

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

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form, 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 will 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.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A consent form describing in detail the device, study procedures, and risks will be provided to each participant. Written documentation of informed consent will be required prior to starting the study. The consent form is included with this protocol. There is only one consent form which covers screening procedures and all other study procedures.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that will be initiated prior to the individual's agreeing to participate in the study and will continue throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. The consent form will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All 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. Participants will have an opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have an opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

Participants in this clinical trial will be visually impaired or blind and may either have varying levels of difficulty in seeing the print on the hard copy consent form or may be totally unable to see the print. The following measures will therefore be implemented to ensure that all participants are able to independently access and review the information in the consent form. Participants will be allowed to use any assistive device they normally use to access printed documents such as optical magnifiers or video magnifiers. An electronic copy (pdf) of the consent form will be available for participants who prefer to view the document using magnification on their computer screen, or text-to-speech output. Braille copies of the consent form will be available for participants who prefer to read using Braille.

Each participant will sign the hard-copy informed consent document prior to any procedures being done specifically for the study. The 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 participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care or other rehabilitation care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality will be strictly held in trust by the participating investigators, their staff, and the sponsor. 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.

Only research personnel involved in the project that have completed Protection of Human Subjects training will have access to study records and data. Authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to data forms for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored 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 local IRB and Institutional regulations.

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. The unique identifier codes will be known only to the members of the research group, and will be recorded in a file retained in a locked cabinet. Any electronic data files that would allow subject identification are password protected and on a secure server. All hard copy forms containing individually identifiable private information that is no longer required is shredded. Before the video clips of collision incidents recorded by the collision warning device are reviewed, an algorithm will be applied to automatically detect faces in the pictures and to cover each face with a blurring mask so that they are unrecognizable to assure anonymity. The face of a participant will never be in any of the pictures because he/she will be wearing the device.

All data will be stored and analysed at Schepens Eye Research Institute.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

N/A

13.5 FUTURE USE OF STORED SPECIMENS

N/A

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All data will be obtained by non-invasive methods and will include data captured on paper records and electronic data recorded by the collision warning device. Data that will be captured on paper records will include vision measures (e.g., visual acuity, visual fields), demographic details, results from cognitive tests (e.g., Short Portable Mental Status Questionnaire, and the Bells test and Schenkenberg line bisection test for visual spatial neglect), responses to questionnaires (the Independent Mobility Questionnaire and the device questionnaire), and data on adverse events. Data entered on the paper

records at each study visit will be transferred to a customized electronic study spreadsheet (database) in a timely manner (within one week of the study visit).

The electronic study spreadsheet and electronic data from the collision warning device will be stored on a secure password protected server and on password-protected desktop computers of research personnel involved in the project. Hard copy record sheets that do not contain personally-identifiable information will be stored in study binders in locked offices (these record sheets use subject identifier codes). Hard copy record sheets that contain personally-identifiable information (such as consent forms and referral letters) will be stored in a locked file cabinet in a locked office. All hard copy forms containing individually identifiable private information that is no longer required will be shredded.

Data collection will be the responsibility of the clinical trial staff at Schepens under the supervision of the PIs. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data integrity and quality will be monitored on an ongoing basis by a second researcher, not responsible for original data entry. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

14.2 STUDY RECORDS RETENTION

Study documents will be retained for the length of time required by institutional policies and by the sponsor (Department of Defense). If applicable, no records will be destroyed without the written consent of the sponsor.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff.

Major Violation/Deviations are any unapproved protocol change that may impact subject safety, affect the integrity of study data, and/or affect subjects' willingness to participate in the study. Major deviations will be reported to the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office within seven (7) working days of discovery.

Minor Violation/Deviations are any unapproved protocol change that does not impact subject safety, compromise the integrity of study data, and/or affect subjects' willingness to participate in the study. Minor deviations will be reported to the local IRB and the USAMRMC, Office of Research Protections, Human Research Protection Office on an annual basis, as part of the annual IRB review of the protocol.

It will be the responsibility of the PIs to determine whether an unapproved Violation/ Deviation from the approved protocol is major or minor and to ensure proper reporting to the IRB. The report will clearly state why the Violation/ Deviation occurred and provide justification for major or minor determinations, and will indicate any corrective actions developed, when necessary. Corrective actions will be implemented promptly.

In the event a change is implemented to eliminate apparent immediate hazard to the subject, the PI report it to the local IRB no later than 24 hours after it is implemented.

14.4 PUBLICATION AND DATA SHARING POLICY

The study will be registered on ClinicalTrials.gov. Results of the clinical trial will be made available to the research community and the public at large by publication in peer-reviewed journals, presentations at international research conferences, and by posting on ClinicalTrials.gov

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The two co-PIs, Dr. Bowers and Dr. Luo will govern the conduct of the study. They will meet on a regular basis.

16 CONFLICT OF INTEREST POLICY

Any conflict of interest of persons who have a role in the design, conduct, analysis, or publication of results from this trial will be disclosed and managed following policies and procedures of the Massachusetts Eye and Ear / Partners Healthcare. Persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

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