STUDY PROTOCOL: 2020-0632 **NCT04420949**

Study Title:
High-precision Immersive Robotic Environment for Sensorimotor Training

Protocol Version:
July 30, 2021, Version 4

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Plain Language Summary:

Falls are a major concern for people living in countries all over the world. Tens of millions of people who fall are seriously injured and hundreds of thousands of people who fall die every year. People who are dizzy are far more likely to fall. The researchers are particularly interested in working with people whose dizziness is caused by looking at checkerboard patterns, walking through grocery store aisles, riding in vehicles, or watching movies (visually-induced dizziness) since this problem affects adults who are healthy and adults who have a variety of health conditions. No diagnostic tests for this condition exist at this time and the treatments currently being used may result in worsening dizziness. This is a preliminary study of how human beings control balance and how symptoms of visually-induced dizziness may result in falls. The researchers created new tests of orientation and balance, as well as a new treatment for visually-induced dizziness. It is not known whether the new tests of orientation and balance are better, worse, or the same as existing tests in the ability to detect problems, nor is it known if the new treatment technique is any better, worse, or the same as existing treatments for dizziness and imbalance. However, the researchers believe that the new tests do improve the ability to detect problems. They also think that the treatment will result in less dizziness, better balance, and reduced risk of falling for those who receive it and that is it a better alternative to treatments that are already available to patients. In order to see if this is true, the researchers will use the new tests and treatments with healthy adults and adults who are affected by dizziness. All the people in this study will undergo the same tests and will receive the same treatment. Testing is done twice before and twice after the treatment period. The treatment is provided twice a week for three weeks in a row. The tests and treatments are done while standing on a computerized platform that measures balance and can tilt people from side to side. During these study procedures, participants wear virtual reality goggles that show them simple images in an otherwise dark environment. The goal of the tests and the treatment is for people to use what the feel to help them decide if the images shown inside the goggles are aligned with the person's sense of gravity. Participation in this study is voluntary and people who decide to participate may stop at any time without penalty. All people in this study will receive a modest payment as reimbursement for their time and effort.

ADMINISTRATIVE INFORMATION

Trial Registration: This trial will be registered with ClinicalTrials.gov after Health Science Institutional Review Board Approval are secured.

Primary Register: ClinicalTrials.gov

Unique Trial ID: NCT04420949

Date of Registration: 5/15/20

World Health Organization Trial Registration Data Set:

Funding Sources: UW-Madison Institute for Clinical and Translational Research, National Institutes of Health

Primary Sponsor: Investigator-initiated, Kreg G. Gruben, PhD

Secondary Sponsor: University of Wisconsin-Madison

Roles of Primary and Secondary Sponsors: Drs. Gruben, Rosenberg, Pyle, Heiderscheit, Whitney, and Grove are ultimately responsible for study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Data and Safety Monitoring: The study team is responsible for data and safety monitoring.

Contact Person: Kreg G. Gruben, PhD Lead Principal Investigator: Kreg G. Gruben, PhD

Public Title: Sensory Training for Visual Motion Sickness

Scientific Title: High-precision Immersive Robotic Environment for Sensorimotor Training

Research Ethics Board Approval: UW-Madison Health Sciences IRB, May 29, 2020

Disease or Condition Studied: Visually-induced dizziness (motion sickness)

Intervention: Sensory re-weighting

Inclusion and Exclusion Criteria: See below.

Study Type: Non-randomized, controlled

Date of First Enrollment: Pending

Target Sample Size: 30

Recruitment Status at Time of CT-UID Request: Not yet enrolling

Primary Outcome(s):

1. The mean of absolute value of the error in rod alignment in each body position tested for the following measures will be used to assess for any treatment effects on verticality perception: ***Rod and Disk Test (RDT)*** (1), ***Subjective Visual Vertical (SVV)*** *(1)* Test, and the ***Rod and Frame Test (RFT****) (1).*
2. The ***Multisensory Balance Evaluation (MBE)***, which is a test that is designed to assess the contributions of somatosensory, visual, and vestibular inputs to standing balance.

Secondary Outcome(s):

3. ***Visual Vertigo Analogue Scale (VVAS (2)):*** average scores will be used as a measure of the intensity of visually-induced dizziness.

4. *The **Vision-related Dizziness Questionnaire (VRD-25)** (3) (frequency and intensity sub-scale scores and total score) will also be used as a broad measure of the impact of visually-induced dizziness and imbalance on daily activities. Collected via web.*

5. *The **Dizziness Handicap Inventory (DHI)** (4) total score will be used as a measure self-perceived disability secondary to dizziness.*

Additional Measures:

6. *The **Activities-specific Balance Confidence Scale (ABCS)** (5) average score will be used to measure self-reported, balance-related confidence.*

7. *The **Vestibular Activities and Participation Measure (VAPM) (6)** average score will be used to assess the impact of vestibular dysfunction on daily activities and participation in life roles.*

8. *The **Vestibular Rehabilitation Benefits Questionnaire (VRBQ) (7,8)** total score will be used to assess participant's perception of the benefits of participating in the treatment program.*

9. *The **Functional Gait Assessment (9)**:* total score will be used as a measure of balance during walking.

10. *Walking Speed* will be measured using a 10-meter walk test

Study Team:

Kreg. G. Gruben, PhD
University of Wisconsin-Madison, Departments of Kinesiology, Mechanical Engineering, and Biomedical Engineering
Role: Principal Investigator (PI)
Contributions: trial oversight, methods development, study design, data collection, data analyses, scientific writing

Ari Rosenberg, PhD
University of Wisconsin-Madison, Department of Neuroscience
Role: Co-investigator (Co-I)
Contributions: methods development, study design, scientific writing

G. Mark Pyle, MD
University of Wisconsin-Madison, Department of Surgery
Role: Co-I
Contributions: study design, recruitment and referrals, adverse and serious adverse events consultation, scientific writing

Bryan C. Heiderscheit, PT, PhD, FAPTA
University of Wisconsin-Madison, Departments of Engineering and Orthopedics and Rehabilitation
Role: Co-I
Contributions: study design, data analyses, and scientific writing

Susan L. Whitney, DPT, PhD, NCS, ATC, FAPTA
University of Pittsburgh, Department of Physical Therapy
Role: Co-I
Contributions: study design, scientific writing

Colin R. Grove, PT, DPT, PhD
Johns Hopkins University, Department of Otolaryngology-Head & Neck Surgery
Role: Co-I
Contributions: methods development, study design, recruitment and enrollment, data collection, data analyses, scientific writing

INTRODUCTION:

Specific Aims:

The World Health Organization reports that **37.3 million falls warrant medical attention** and an estimated **646,000 persons die because of falling** worldwide each year. One significant risk factor for falls is **dizziness**, which, according to epidemiological data, is associated with a **12-fold increase** in the likelihood of falls. Given the strength of this association, there is a pressing need to intervene in the connection between dizziness and falls in order to reduce morbidity and mortality.

From a physiological and biomechanical perspective, preventing falls requires sensing **postural orientation** to maintain **postural equilibrium**. Due to sensor redundancy, individuals have sensory integration preferences that influence their postural orientation. Tests of verticality perception, such as the Subjective Visual Vertical Test, Rod and Frame Test, and Rod and Disk Test are commonly used to assess orientation. Postural equilibrium, on the other hand, which is influenced by a myriad of individual, task, and environmental factors, is commonly assessed by analyzing center of pressure (COP) data, as when interpreting the Sensory Organization Test.

Unfortunately, each of these tests has significant shortcomings that affect their diagnostic accuracy and, thus, limit their clinical utility. Tests of verticality perception may not reveal impairments if conducted only with the patient in an upright posture. Additionally, COP-based tests provide an incomplete characterization of postural equilibrium control. As a result of these and other inadequacies, these gold-standard tests fail to consistently identify persons with dizziness and those who are at risk for falls or recurrent falls. **In this proposal, we introduce** 1) **a verticality perception test battery** that leverages virtual reality (VR) and robotics **and** 2) **a postural equilibrium test battery** that uses the Intersection Point (IP) of the ground reaction force (GRF) as the outcome for a complete characterization of postural equilibrium control.

Persons affected by certain health conditions, including Alzheimer's disease, vestibular loss, stroke, and traumatic brain injury, as well as older adults and even some otherwise healthy individuals experience disorientation and disequilibrium. **One common type of dizziness reported across these populations is visually-induced dizziness**, which is triggered by visual stimuli such as busy patterns or moving scenes. The cause of visually-induced dizziness is believed to be **visual dependence**, a perceptual style that may be either developmental or acquired. Studying persons with this specific type of dizziness provides us unique opportunities to pursue our **long-term goals** to advance understanding of normal postural orientation and equilibrium, as well as the association between dizziness and falls.

The current standard of care for persons with visually-induced dizziness is optokinetic stimulation (repeated exposure to complex patterns and moving images). Though initial efficacy trials of this intervention were positive, results from subsequent effectiveness trials are less clear. This modality has also proven to be difficult to implement in practice due to a lack of clarity regarding treatment parameters, optimal delivery methodologies, and who will most likely benefit. As a result, use of optokinetic stimulation often results in exacerbation of symptoms and/or early withdrawal from treatment. Herein, **we introduce a promising intervention** based in part on sensory re-weighting theory and findings from preliminary work in primate and human models of bilateral vestibular ablation.

Our **central hypothesis** for this study is that intensive sensory re-weighting training will result in reduced visual dependence in healthy persons and those with visually-induced dizziness. In order to achieve this outcome, we developed these **specific aims** in the context of a phase I efficacy trial.

1. Assess the accuracy, sensitivity, and specificity of VR-based robotic verticality assessments.
We will calculate the accuracy, sensitivity, and specificity of each verticality perception measure conducted while standing upright or tilted leftward or rightward in the frontal plane.

2. Determine the potential diagnostic value of IP, a postural equilibrium measure.
The IP curves of healthy persons and symptomatic persons will be significantly different (Hypothesis A).

3. Demonstrate the effects a novel sensory re-weighting intervention.

The intervention will result in reduced symptoms (Hypothesis B) and improved verticality perception (Hypothesis C). Also, changes in balance control will be detected by pre-post comparisons of the IP curves measured during visual-vestibular conflict (Hypothesis D).

Background and Rationale:

Falls result in significant morbidity for both younger and older adults and falls are the second leading cause of accidental or unintentional mortality worldwide (10). Fatal falls are most common in persons over 65 years old. Data from the United States shows that one out of five falls results in serious morbidities, such as a fracture or traumatic brain injury (11). A recent analysis of mortality data(12) reveals 29,666 Americans age 65 and older had a fatal fall in 2016. That same year, Wisconsin's fall-related death rate of 142.7 per 100,000 was the highest in the nation(12). Despite multidisciplinary efforts to address this public health crisis over the past two decades(13,14), the overall rate of fatal falls in older adults increased by 31% from 2007 to 2016(12). Thus, the need to improve knowledge about human balance control and falls prevention is more urgent than ever.

The issue of falls is a complex problem and many risk factors must be considered when designing falls prevention strategies. Strong associations exist between current and future falls and a history of falls, gait problems, walking aid use, vertigo, Parkinson's disease, and antiepileptic drug use(15). We are particularly interested in vertigo (dizziness) which is the third most common symptom reported in ambulatory settings(16) and has a strong association with falls as measured by a common test of sensory interaction in balance(17). We believe developing better methods of evaluating and treating patients with dizziness and imbalance is crucial to addressing this global public health crisis.

Our attention is focused on visually-induced dizziness because this condition is unique in that it cuts across populations, affecting persons with cognitive impairments, sensory system disturbances, and neurological conditions, as well as otherwise healthy adults and those who are experiencing physiological changes associated with ageing. Studying persons with visually-induced dizziness provides a model for advancing understanding the sensorimotor processes underlying human postural orientation and postural equilibrium, as well as the association between dizziness and falls.

A diagnostic test for visually-induced dizziness does not exist. Though this condition is believed to be the result of visual dependence(18) (excessive weighting of visual cues), the gold-standard tests of verticality perception (Rod and Frame Test (RFT)(19)) and postural equilibrium (Sensory Organization Test (SOT)(20)) are inadequate surrogates for measuring visually-induced dizziness. In one study of adults with visually-induced dizziness, 50% of patients had abnormal SOT results and just 15% scored outside the normal range on the RFT(21), both of which are proposed to detect preferences for visual cues. Better diagnostic tools are needed so more patients may be identified and appropriately treated.

We developed new testing methods after considering the limitations of current methods of verticality and balance. One prominent issue regarding verticality tests is that these tests are typically performed with the patient's head upright. Multiple authors have established that tests of verticality perception often fail to detect abnormalities in patients with known impairments when conducted this way(22-24). Our most significant concern regarding the SOT (and others like it) is that these tests only reveal half of the story regarding how the nervous system controls postural equilibrium because only center of pressure (COP) data is analyzed while the effects on the body of the direction of the ground reaction force are completely ignored. Our methods eliminate these problems.

In the mid-1990s, optokinetic stimulation was shown to reduce dizziness and improve balance in persons with unilateral and bilateral vestibular loss(25,26). It wasn't until a decade later that this technique became popularized among physical therapists following a landmark trial in patients with chronic dizziness (27). The results of subsequent studies suggest that this technique does not work for

all patients(28,29) nor is it necessarily superior to usual care with vestibular rehabilitation(30). Unfortunately, experience with the technique reveals some patients are prone to adverse events.

With these data in mind, we developed an alternative intervention. We constructed a theoretical framework based on prior work that demonstrates a) there is an association between impaired verticality perception and falls(31), b) Subjective Visual Vertical is modifiable in health(32) and disease(22,33,34), c) sensory re-weighting training that upregulates somatosensory cues for postural orientation resulted in decreased dizziness and improved balance in a case of complete bilateral vestibular loss(35) and reduced visual dependence in monkeys with bilateral vestibular ablation[Rosenberg, et al., unpublished data], d) and rehabilitation of orientation in a case of stroke is task-specific(36). We now propose a new method to address the effects of impaired verticality perception on postural orientation and postural equilibrium which we believe will prove to be safer and more effective than optokinetic stimulation and that has broad applicability in balance rehabilitation.

Objectives:

We developed new methods to assess verticality perception and postural equilibrium, as well as a new method for training orientation and balance. The **specific aims** for this trial are as follows:

1. Assess the accuracy, sensitivity, and specificity of VR-based robotic verticality assessments.
We will calculate the accuracy, sensitivity, and specificity of each verticality perception measure conducted while standing upright or tilted leftward or rightward in the frontal plane.

2. Determine the potential diagnostic value of IP, a postural equilibrium measure.
The IP curves of healthy persons and symptomatic persons will be significantly different (Hypothesis A).

3. Demonstrate the effects a novel sensory re-weighting intervention.
The intervention will result in reduced symptoms (Hypothesis B) and improved verticality perception (Hypothesis C). Also, changes in balance control will be detected by pre-post comparisons of the IP curves measured during visual-vestibular conflict (Hypothesis D).

Trial Design: The study will be conducted in three phases. The first phase is for baseline testing. The second phase is when treatment occurs. The third phase is for follow up testing. Participants will be tested twice during the baseline and follow up phases. Six treatment sessions will occur during the treatment phase. Healthy adults (Group 1, n=15) and adults with self-reported visually-induced dizziness (Group 2, n=15) will undergo the same tests and will receive the same intervention.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Study Setting:

This trial will be conducted at the University of Wisconsin-Madison, a level 1 research institution. Study visits will occur at the Neuromuscular Coordination Laboratory, Kreg Gruben, PhD, Director.

Eligibility:

Healthy Participants:

Inclusion Criteria: Participants must 1) be adults between the ages of 18 and 79 years old, 2) have normal self-reported cognitive function, 3) speak English fluently, 4) weigh less than 225 pounds and be less than 6’4”, 5) be able to support their body weight in an upright posture for 15 minutes at a time, and 6) be able to follow the guidelines regarding permitted and prohibited additional treatments outlined in this protocol.

Exclusion Criteria: Participants must not 1) be pregnant or planning to become pregnant while in "on study" status, 2) have best-corrected visual acuity > 20/70, 3) have a self-reported, uncompensated, binocular vision abnormality, such as strabismus, amblyopia, or diplopia, 4) have peripheral neuropathy, and/or 5) have a self-reported history of frequent syncope (>1/month).

Participants with Visually-induced Dizziness:

Inclusion Criteria: Participants must 1) be adults between the ages of 18 and 79 years old, 2) have self-reported symptoms of visually-induced dizziness, 3) have normal self-reported cognitive function, 4) speak English fluently, 5) weigh less than 225 pounds and be less than 6'4", 6) be able to support their body weight in an upright posture for 15 minutes at a time, and 7) be able to follow the guidelines regarding permitted and prohibited additional treatments outlined in this protocol.

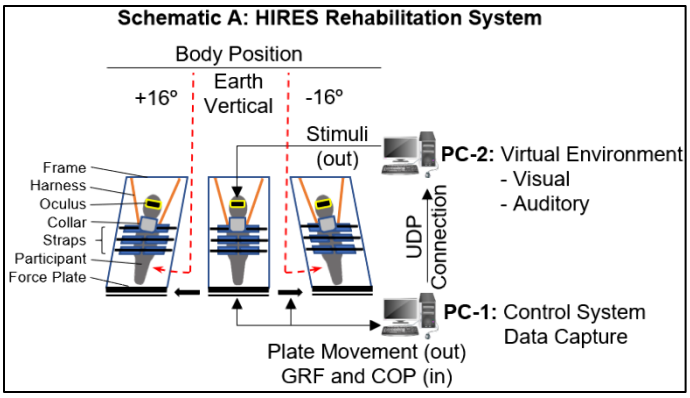
Exclusion Criteria: Participants must not 1) be participating in vestibular and balance rehabilitation therapy and/or be pregnant or planning to become pregnant while in "on study" status, 2) have best-corrected visual acuity > 20/70, 3) have a self-reported, uncompensated, binocular vision abnormality, such as strabismus, amblyopia, or diplopia, 4) have peripheral neuropathy, and/or 5) have a self-reported history of frequent syncope (>1/month).

Further Information Regarding Exclusions for Special Populations: Individuals who lack capacity to consent will not be enrolled as these individuals would either have neurological impairments that would preclude accurate data collection or would be too physically debilitated to participate in this research. Women who are known to be pregnant will be excluded since changes in body morphology associated with pregnancy impact postural control and would confound our results and the body support system used in this study may not be comfortable for a pregnant woman. Those individuals who are non-English speaking or who have limited understanding of the English language will be excluded given the inherent difficulty in translating the instructions for study-related procedures and the lack of translation services available to the study team.

Intervention:

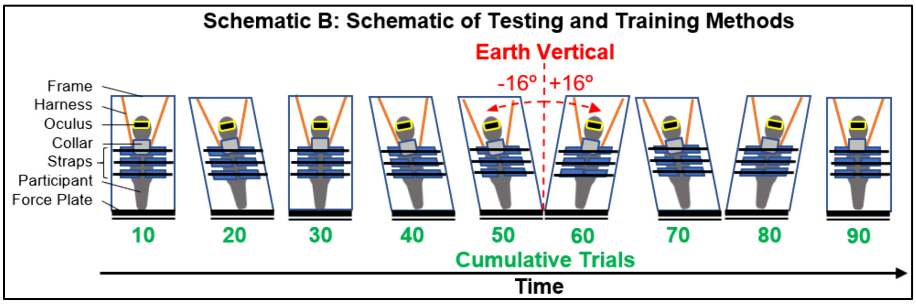
High-precision Immersive Robotic Environment for Sensorimotor (HIRES) Rehabilitation:

Testing and Training System: Testing of verticality perception and the sensory re-weighting training will be conducted with the High-precision Immersive Robotic Environment for Sensorimotor (HIRES) Rehabilitation System (Schematic A). The HIRES Rehabilitation System is a partially automated system consisting of hardware (a Kinetic Immersive Interfaces for Neuromuscular Coordination Enhancement (KIINCE)(37), a custom-built body support system, a VR system, and 2 PCs) that is integrated using software (proprietary code in LabVIEW; Oculus VR; and Unity 3D). PC-1 is used as the primary controller and data collection tool. A robotically controlled force plate from a re-engineered KIINCE is used as a body transport device for testing and training. PC-1 controls PC-2 through a user datagram protocol linkage. PC-2 in turn controls the VR system (Oculus Rift, Oculus VR, Menlo Park, CA, USA), which is used to provide auditory instructions and present visual stimuli during testing and training. A translucent film is placed over the VR lenses in order to eliminate potentially visually orienting cues that could be gleaned from pixilation of the image.



Description of the Testing and Training Environment: Participants will be supported in quiet standing by a safety harness and crisscrossing strap system that minimizes cues to postural orientation from somatosensory receptors along the body segments in contact with the straps. A cervical collar is used to maintain consistent alignment between the head and trunk. The VR headset is used to create a virtual environment with auditory masking in order to eliminate orientation cues from visual references or ambient sound. Once participants are in position, we familiarize them with being tilted, the visual stimuli used in testing and training, and how to operate a hand-held response device. The core task that participants are required to perform during verticality tests and training is to discern the direction of gravity without using visual or auditory cues. In each situation, the image of a rod will be presented at a pre-determined angle and the participant must determine if the rod is aligned with their estimation of gravity. Participants will view 5-minute instructional video prior to the start of the first session.

Participant Positioning During Testing and Training: Three different body positions will be used during testing and training; earth-vertical and clockwise and counterclockwise tilted 16º in the frontal plane (Schematic B). Which position a participant is in for a given set of test or training trials is predetermined by a pseudorandomized sequence generator.



Presentation of the Visual Stimulus and Method for Participant Response (Testing): During each testing trial, the image of a rod (Figure 1) will be displayed in one of three VR environments: Subjective Visual Vertical (Figure 3), Rod and Frame (Figure 4), and Rod and Disk (Figure 5). The rod initial presentation angle for a given test trial will be determined based on a predetermined, pseudorandomized array of possible angles between +/- 20º and +/- 70º from earth-vertical. A new array is generated for each time the test is performed. Participants will use the dial on the response box to rotate the rod until it lines up with their estimation of gravity and then press the button to record their response. Participants will not receive any feedback regarding whether their responses are correct or incorrect during testing.

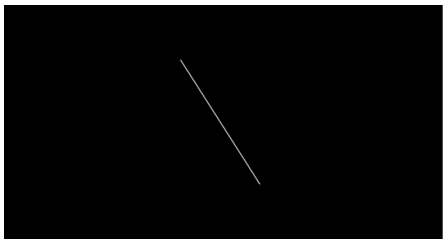


Figure 1: Rod Stimulus

Presentation of the Visual Stimulus and Method for Participant Response during (Training): During each training trial, the image of a rod (Figure 1) will be displayed in a void VR environment. As in a typical VR environment, the head-mounted visual display is modulated to appear stationary in the laboratory reference frame despite head movement. The rod initial presentation angle for a given trial will either be 0º (earth-vertical) or selected sequentially from an array of 20 values derived using a logarithmic scale, starting at +/- 60º and ending with +/- 1º from earth-vertical. This array was predetermined and will be the same for all participants and all rounds of training. These 20 rod angle values correspond to 20 different levels of difficulty. Large rod angles are easier to detect as different from earth-vertical than are small rod angles. Participants will use the response box to indicate which direction they think the rod would need to rotate for it to be aligned with their perception of gravity.

Description of the Training Task: During training, sensory re-weighting will be driven by priming upregulation of somatosensory cues. Two rounds of training, each lasting approximately 15 minutes and block-randomized in sets of 10 trials, will be conducted per training visit. Between each round of training, participants will rest in either sitting or standing (based on participant preference) and the VR headset will be removed. Rest breaks will last approximately 5 minutes.

In each training trial, participants must determine the direction of gravity and then indicate if the rod being displayed is aligned with gravity or if it needs to rotate clockwise or counterclockwise for that to be so. Participants will be instructed to pay attention to what they feel from their feet, legs, and gut during training and to use that pressure, stretch, movement, and muscle tension feedback to help them sense gravity. Participants will use the dial on the response box to record their responses. A button press indicates the respondent believes the rod is oriented with gravity. A greater than 10º of rotation of the dial clockwise or counterclockwise indicates the respondent believes that is the direction the rod would need to rotate to be in line with their estimation of gravity.

Criteria for Stopping a Round of Training: Each round of training will continue until the participant requests to rest, their performance plateaus for 20 trials at a given level of difficulty, or a maximum of 15 minutes has elapsed.

Response Feedback: Immediate auditory and/or non-orienting, visual feedback will be provided after each training trial. A correct response results in the auditory cue, “correct” being played through the headset. An incorrect response results in the auditory cue, “incorrect” being played through the headset and non-orienting visual feedback that indicates the direction the rod would need to rotate for it to align with the direction of gravity. See Figure 2 for an example of feedback.

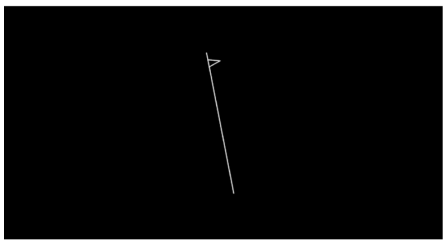


Figure 2: Example of Response Feedback. The participant would hear “incorrect” and see the arrowhead pointing to the right indicating the rod needed to rotate clockwise in order to be aligned with gravity.

Progression of the Training: The level of difficulty for each training trial is related to the 20 different rod tilt angles, as described above. Each round of training begins at difficulty level 1. A staircase method is then used to adapt the level of difficulty based on response accuracy. After two consecutive correct responses, the difficulty increases. After each incorrect response, the difficulty decreases. The highest level of difficulty achieved within a round of training is determined by what the participant achieves within the 15-minute time limit.

Definition of Adherence:

Appropriate adherence to the intervention is defined attendance of at least 4 out of 6 intervention visits and/or completion of 8 rounds of training (~15 minutes each) and/or completing 1,600 individual training trials.

Recruitment and Retention Strategies:

We will publish non-proprietary, study-related information on-line (https://ncl.labs.wisc.edu/) highlighting the ongoing work in the lab. Email will be used for efficient and consistent communication with participants if consent to use email is provided. Participants will receive contacts from the study team with reminders regarding completing the patient-reported outcomes and upcoming study visits. Participants will be offered reimbursement of $25 per visit. A completion bonus of $50 will be offered to any participant who completes all study-related requirements. Total possible reimbursement per participant is $250.

Permitted Additional Treatments:

Participants will be advised to continue taking life sustaining medications and medications prescribed to be taken regularly. Performance of a home exercise program for dizziness and imbalance that was prescribed prior to enrollment is permitted so long as this program is not advanced while the participant is on study.

Prohibited Additional Treatments:

We will ask participants to please avoid taking certain p.r.n. medications (see below) starting 48 hours prior to study visits. These medications are: ANTI-VERTIGO MEDICINE (Antivert, Meclizine, Valium, Scopolamine, etc), SEDATIVES (Nembutal, Seconal, Dalmane, Doriden, Placidyl, Quaalude, Butisol, or any other sleeping pills), and NARCOTICS and BARBITUATES (Phenobarbital, Codeine, Demerol, Dilaudid, Percocet, Percodan, Vicodin, etc). Tylenol (acetaminophen) and Advil (NSAIDS) may be taken for pain as directed by the participants prescriber. These medications or medication classes may interfere with test performance for the outcome measures of this research. It is optimal that participants avoid taking these p.r.n. medications for 48 hours prior to testing.

Withholding these medications or medication classes is standard practice in clinical otolaryngology and audiology practice and the language above is based on similar language provided to patients who are scheduled for vestibular function tests. Participants will be advised to consult with the prescribing provider prior to discontinuing these medications. Should any new and unanticipated signs or symptoms arise while not taking these p.r.n. medications prior to study visits, participants will be directed to contact the prescribing provider as soon as possible.

Participants must not be participating in other treatments for visually-induced dizziness and imbalance while on study since this would confound our results. Prohibited treatments include medications,

homeopathic remedies, and the use of body-worn devices, acupuncture, chiropractic interventions, and active participation in vestibular rehabilitation for dizziness and/or motion sickness and imbalance in which treatment is being progressively advanced.

Consumption Restrictions:

Alcohol, tobacco products, and caffeine may potentially influence the clinical examination or the results of performance-based outcomes. Thus, participants will be encouraged to avoid using alcohol for 48 hours prior to study visits, as well as to avoid consuming food or beverages containing caffeine and tobacco products within 4 hours before a study visit. Requesting that participants withhold tobacco and/or caffeine is analogous to self-restriction of intake of these products for social or health reasons.

Primary and Secondary Outcomes:

The following patient-reported outcome measures will be collected through secure links to the ICTR REDCap database unless otherwise noted below (or on paper if participants decline to use email for study-related purposes):

Patient-reported Outcome Measures:

Visual Vertigo Analogue Scale (VVAS): Time Required: < 5 minutes. The original VVAS(2) consists of nine scales, each relating to a specific symptom-provoking situation. The distance from the zero anchor to the respondent's marking is measured to the nearest 0.5 cm. Items that are not applicable to the individual's life are completed as imagined. Internal consistency and validity of the VVAS have been established(2). A total score is calculated to determine the severity of visual vertigo by summing all items, dividing by the number of answered items, and then multiplying by 10. We will use the total score as the measurement variable for this instrument. The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group. These data will be collected at each assessment timepoint.

Vision-related Dizziness Questionnaire (VRD-25): Time Required: < 5 minutes. The VRD-25(3) is used to quantify vision-related dizziness. This outcome measure consists of 25 questions comprising two subscales [frequency (VRD-12) and severity (VRD-13) of symptoms]. Test-retest reliability for the VRD-25 is well above the good performance level and convergent validity for the VRD-25 was demonstrated with the DHI. Spearman correlation coefficients are 0.75 between the DHI and VRD-12 frequency scale and 0.76 between the DHI and VRD-13 severity scale(3). The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group. These data will be collected at each assessment timepoint.

Dizziness Handicap Inventory (DHI): The DHI (4) is used to assess a person's perceived level of handicap stemming from symptoms of dizziness. This patient-reported outcome measure consists of 25 questions related to physical, emotional, of functional health. Each question is answered as "yes" (dizziness is always a factor), "sometimes" (dizziness is sometimes a factor), or "no" (dizziness is never a factor for a given situation or issue. Responses are scored as "yes" = 4 points, "sometimes" = 2 points, and "no" = 0 points. The maximum score on the DHI is 100 points with higher scores indicating higher levels of perceived handicap.

Activities-specific Balance Confidence Scale (ABCS): The ABCS (5) is a patient-reported outcome measure that consists of 16 questions for which the respondent answers how confident he/she feels in not becoming unsteady or falling in specific situations. Confidence is rated on a scale of 0% to 100% with 0% indicating no confidence and 100% indicating complete confidence in the ability to maintain balance. The ABCS average score is an average of responses across all items. Average scores of greater than or equal to 80% are considered normal for adults (5).

Vestibular Rehabilitation Benefits Questionnaire (VRBQ): The VRBQ (8) was developed to assess outcomes from vestibular rehabilitation. The 22 questions are based on a literature review, patient interviews, and items from other measures. These questions are divided into three sub-scales: dizziness and anxiety (6), motion provoked dizziness (5), and quality of life (11). The total score ranges from 0%-100% and scores > 0% indicate the presence of symptoms, functional loss, or decreased quality of life. See http://www.isvr.soton.ac.uk/audiology/vrbq.htm for more information regarding the scoring methodology. It has been validated against other measures(8). The VRBQ is designed to measure the difference between the patient's current state of symptoms and quality of life compared to a state that is normal for the individual.

Performance-based Outcome Measures:

Verticality Perception Testing (General Information): Time Required: 5 minutes (full test battery). Testing will be conducted in sets of 10 trials while participants are either standing upright or standing while tilted to the left or the right 16°. Once in position, participants will be shown the image of a rod on the screen inside VR the headset. Participants will use a dial on the response box to rotate the rod until it is lined up with the direction of gravity, which they are instructed to think as being the direction an object would fall if they let it drop from their hand to the floor. Once they think the rod is lined up with the direction of gravity, they press the button on the response box to record their response. Participants will be encouraged to try to not second guess themselves and to just rotate the rod to the position they think is upright and press the button. During these tests, the rod will be shown in one of three different test scenes: Subjective Visual Vertical, Rod and Frame, or Rod and Disk. These test scenes will be shown in a predetermined, pseudorandomized order. Every 10 trials, the KIINCE device positions the participant in standing upright or standing while tilted 16° to the left or to the right in the frontal plane. The order of body positions is also predetermined in a pseudorandomized manner. This testing takes about five minutes. These data will be collected at each assessment timepoint.

Subjective Visual Vertical (SVV) with the Oculus Rift: The clinometric properties of the traditional SVV test have been established(1). An image of a rod will be shown in the central portion of the visual field. The surrounding virtual environment will be void (Figure 3). The image is presented in low-contrast, grayscale with low luminance to minimize visual after-effects. A batch of rod angles will be predetermined. The batch has a lower limit of +/- 20° from earth-vertical and an upper limit of +/- 70° from earth-vertical. Researchers will control the initial presentation of the orientation of the rod and participants will use a hand-held device to rotate the rod and then indicate when they believe the rod is oriented to gravitational vertical. This assessment will be completed using an Oculus Rift and without any reference to external visual cues. Only binocular testing will be completed. We will conduct a total of about 30 trials (the exact number of trials performed in each position will depend on the pseudorandomization of the test, and the average value for performance in each position will be used in data analysis). We conduct this test pseudorandomly interleaved with the RFT and RDT. We will use the mean of absolute value of the error in rod alignment measured in degrees for each body position tested as the measurement variable for this outcome. The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group mean.

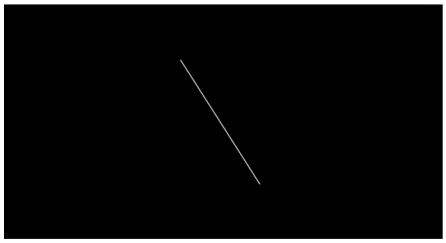


Figure 3: SVV Visual Stimulus

Rod and Frame Test (RFT) with the Oculus Rift: The clinometric properties of the traditional RFT have been established(1). An image of a rod will be projected inside a tilted frame within the central portion of the visual field. The surrounding virtual environment will be void (Figure 4). The image is presented in low-contrast, grayscale with low luminance to minimize visual after-effects. The frame will be tilted by +/- 20° in the frontal plane. A batch of rod angles will be predetermined. The batch has a lower limit of +/- 20° from earth-vertical and an upper limit of +/- 70° from earth-vertical. Researchers will control the initial presentation of the orientation of the rod and participants will use a hand-held device to rotate the rod and then indicate when they believe the rod is oriented to gravitational vertical. This assessment will be completed using an Oculus Rift and without reference to external visual cues. Only binocular testing will be completed. We will conduct a total of about 30 trials (the exact number of trials performed in each position will depend on the pseudorandomization of the test, and the average value for performance in each position will be used in data analysis). The test is conducted pseudorandomly interleaved with the SVV and RDT. We will use the mean of absolute value of the error in rod alignment measured in degrees for each body position tested as the measurement variable for this outcome. The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group mean.

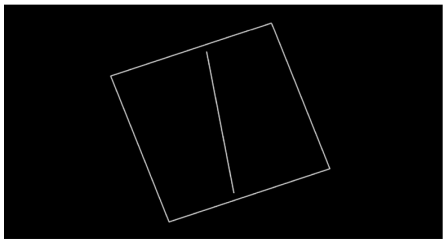


Figure 4: RFT Visual Stimulus

Rod and Disk Test (RDT) with the Oculus Rift: The clinometric properties of the traditional RDT have been established(1). The image of an annulus comprised of a pseudorandomized pattern of dots will be presented in the VR headset. The image of a rod is also presented within the central region of the annulus that is black (Figure 5). The entire image is presented in low-contrast, grayscale with low luminance to minimize visual after-effects. This image will be rotated at 30° per second in either a clockwise or counterclockwise direction around the participant's line of sight. An image of a rod will be projected into the central portion of the annulus. A batch of rod angles will be predetermined. The batch has a lower limit of +/- 20° from earth-vertical and an upper limit of +/- 70° from earth-vertical. Researchers will control the initial presentation of the orientation of the rod and participants will use a hand-held device to rotate the rod and then indicate when they believe the rod is oriented to gravitational vertical. This assessment will be completed using an Oculus Rift and without reference to external visual cues. Only binocular testing will be completed. We will conduct a total of about 30 trials (the exact number of trials performed in each position will depend on the pseudorandomization of the test, and the average value for performance in each position will be used in data analysis). The test is conducted pseudorandomly interleaved with the SVV and RFT. We will use the mean of absolute value of the error in rod alignment measured in degrees for each body position tested as the measurement variable for this outcome. The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group.

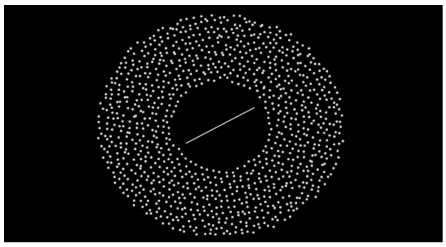


Figure 5: RDT Visual Stimulus

Multisensory Balance Examination (MBE): Time Required: 20 minutes. This test was developed for this research project. It is designed to assess balance during quiet standing in different sensory conditions. The visual conditions are either 1) eyes open or 2) eyes closed. The visual environment conditions are either 1) blank virtual world, 2) vertical line (Figure 6), 3) static, tilted frame (Figure 7), or rotating annulus (Figure 8). The visual environment is controlled using an Oculus Rift. The surface conditions are either 1) non-compliant or 2) compliant (4-inch-thick medium density T-foam). All trials are performed while standing on a force plate with the feet in a self-selected, comfortable position. Subjects perform one trial (lasting 50 seconds) of each condition. The force plate samples COP and direction of ground reaction force. The frequency-dependent height of the Intersection Point (IP)(38) of the ground reaction force is the main outcome derived from this test. For this research, we will study the characteristics of the IP curvature plot for each test trial (See Boehm, et al. 2019 a complete description of this metric). We will also compare the IP curvature for certain conditions versus others in order to assess the impact of manipulating specific sensory inputs on the behavior of the IP. From each comparison, we will be able to explore the contributions of different senses to IP behavior. We will use the IP curves as the measurement variables for this outcome. The analysis metric will be the difference between pre-test and post-test measurement within subjects and by group.

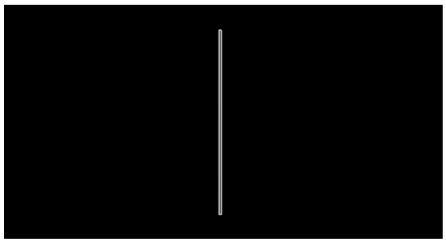


Figure 6: MBE Stationary Vertical Rod Stimulus

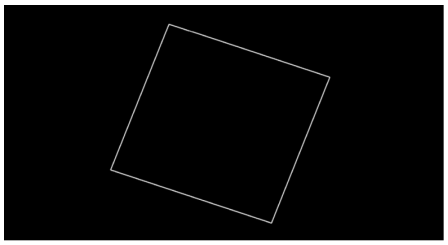


Figure 7: MBE Tilted Frame Stimulus

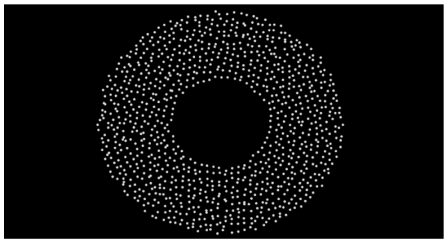


Figure 8: MBE Rotating Annulus Stimulus (dot pattern rotates at 30 degrees/second)

Additional Measures:

Functional Gait Assessment (FGA): The FGA (9) consists of 10 gait-related items, each being scored on a ordinal scale from 0-3. Thus, the total possible score on the FGA is 30. Test items include walking, walking with head turns, walking heel-to-toe, and walking with eyes closed. This test will be conducted along a 20-foot path in a designated area with markings on the floor that facilitate appropriate scoring based on gait deviations from a straight path. The psychometric properties of the FGA are described elsewhere (9). The FGA will be conducted in accordance with the methods of the original publication (9).

Gait Speed: A 10-meter walk test will be conducted with eyes open and eyes closed in accordance with previously published methodology(39). Participants will be allowed one practice trial for each condition.

Participation Timeline:

Including a telephone screening, there are 9 study contacts over 6 weeks. Questionnaires, as well as tests of verticality perception, balance, and gait are to be collected in weeks 1, 2, 4, and 5 (see Table 2, page 19). The intervention will be conducted 2 times during each twice-weekly visit in weeks 2, 3, and 4. This research is being conducted in the UW-Madison Neuromuscular Coordination Laboratory.

In order to substantially reduce the time each participant is required to be in the lab and increase accuracy of data collection, patient-reported outcomes will be administered via ICTR REDCap. Measures will be collected up to 24 hours before visits 1 and 2, as well as up to 24 hours after visit 3, and up to 24 hours before visit 4 in order to ensure patient-reported and performance-based outcomes are administered at the same time points. Pre-testing with the performance-based outcomes described in this protocol will occur at visit 1 and immediately prior to training during visit 2. Post-testing with the performance-based outcomes will take place immediately after training during visit 7, as well as during visit 8. The intervention will be provided during visits 2 and 3. The data collected at each time point is shown in Table 3.

Participants will be in “on treatment” status during weeks 2-4. “Off study” status coincides with the completion of post-testing.

Table 2: Participation Timeline:

Activity	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
Screening Outcomes Training	Before enrolled	Baseline 1	Baseline 2 2x/week	2x/week	Post-test 1 2x/week	Post-test 2

Table 3: Data Collected at Each Assessment Timepoint

Measure	Pre-test 1	Pre-test 2	Post-test 1	Post-test 2
VVAS	X	X	X	X
VRD-25	X	X	X	X
ABCS	X	X	X	X
DHI	X	X	X	X
VAPM	X			X
VRBQ	X			X
SVV	X	X	X	X

RFT	X	X	X	X
RDT	X	X	X	X
MBE	X	X	X	X
FGA	X			X
Gait Speed	X			X

Sample Size:

We based sample size on Whitehead et al,(40) (pg. 1071, Table 8) who recommends a sample size of 15 subjects per group for a efficacy trial when the main trial is expected to generate a medium-sized standardized mean difference of 0.3 to 0.7 at 90% power. Subjects who withdraw for any reason will be replaced. All analyses will be conducted once the last participant completes participation.

Recruitment:

Recruitment (Background): Motion sickness is an extremely common phenomenon, particularly in persons with vestibular disorders. Data regarding the prevalence of visually-induced motion sickness is limited. The prevalence of motion sickness varies based on factors such as age, gender, nationality, occupation, etc (41). One-third of adults in the general population report they experience such symptoms(42). Similarly, Strupp, et al.(43) found nearly one-third of persons presenting to a tertiary center for vertigo reported a history of motion sickness. They concluded that motion sickness is a relevant comorbidity for persons with vestibular disorders. Thus, we anticipate being able to quickly recruit the suggested number of participants from UW Health, UW-Madison, and the surrounding community within 6 months of opening.

Indirect recruitment by posting advertisements (See attached file: HIRES Efficacy Trial Study Ad V1): Advertisements will be posted in the waiting rooms of the University of Wisconsin Hospital and Clinics (UWHC), Ear, Nose, and Throat (ENT) Clinic, clinics affiliated with the UWHC Department of Orthopedics and Rehabilitation (UW Health at the American Center, Yahara Clinic, Clinical Sciences Center, Research Park Spine Clinic and Sports Rehabilitation Clinic, and Middleton Rehabilitation Clinic), and on bulletin boards within the University of Wisconsin-Madison (UW-Madison) Department of Kinesiology, Occupational Therapy Program, and Physical Therapy Program. Permission to post advertisements will be obtained from Katina Kauffman, RN, Clinical Manager of Otolaryngology; Kip Schick, Director, Department of Orthopedics and Rehabilitation, Gary M. Diffee, PhD, Chair, Department of Kinesiology; and Lisa Steinkamp, Director, Physical Therapy Program. Dr. Grove

will ensure that postings follow applicable policy and are removed after enrollment is closed.

Targeted emails will be sent to past participants who were enrolled in the study, “Reliability and Validity of a Next-generation Sensory Organization Test,” IRB #2017-1081. Our prior IRB approval allowed for the retention of certain data to use for contacting those participants to invite them to participate in future research. We will send up to three recruitment emails inviting those subjects who self-identified as having visually-induced dizziness on the VVAS.

Targeted email campaigns will be sent to students, faculty, and staff associated with the UW-Madison Physical Therapy Program, Occupational Therapy Program, and Department of Kinesiology: The UW-Madison Department of Information Technology (DoIT) Mass Email service may be employed to recruit participants from the UW-Madison campus community. The educational experience of students in these programs may be enhanced by learning more about patient-reported and performance-based outcome measures utilized in this research. Faculty and staff may benefit by being exposed to research capabilities within the Departments of Kinesiology and Orthopedics and Rehabilitation as this could lead to generating ideas for future collaboration. Potential benefits regarding possible treatment effects

are described elsewhere. Dr. Gruben is an Associate Professor in the Department of Kinesiology and, therefore, may have a status relationship with individuals from the Department of Kinesiology. Dr. Grove was, therefore, be directly involved with recruiting and enrolling individuals associated with the Department of Kinesiology prior to enrollment closing. Dr. Gruben's involvement in recruitment and enrollment will be consistent with his COI management plan. Dr. Heiderscheit is a Professor in the Physical Therapy Program and will be blinded to whether or not any physical therapy students participate in this research. The mass email program provided by DoIT will be utilized to send these emails. The Health Sciences Institutional Review Board (HS-IRB) guidance for sending mass emails will be followed. One email will be sent per month until the required number of participants has been recruited.

Targeted email campaigns will be sent to clinical staff associated with the UWHC Department of Orthopedics and Rehabilitation: Research currently amounts to a small percentage of activity within this department; so, staff are generally not familiar with the conduct of research. Staff within the department may benefit from participating in this research by learning more about the research process and the specific outcome measures utilized in this research. Experiencing the rigor with which these outcome measures are administered as part of a research study may motivate staff to conduct these and other measures with similar rigor in clinical practice which may, in turn, result in a higher standard of care. Additional benefits regarding possible treatment effects are described elsewhere. G. Mark Pyle, MD is a referral source for this department; however, he does not hold a status relationship with members of the department. Dr. Grove was a member of this department; however, he did not have a supervisory role within the department; thus, he does not have a status relationship with department staff. Dr. Grove was responsible for utilizing departmental email distribution lists to send recruitment emails. This procedure was approved by Lisa Risberg and permission to send email campaigns was obtained from Kip Schick, Interim Director, Department of Orthopedics and Rehabilitation. One email will be sent per month until the required number of participants has been recruited.

Direct recruitment and referral of patients: The following procedures will be utilized in the clinic settings listed below. Providers, as well as clinic staff, will be made aware of general study eligibility criteria and will identify their own patients who may be eligible via the daily clinic schedules and will inquire of potential participants if they are interested in learning more about this research. If a patient indicates interest in learning more, the provider and/or clinic staff will either get permission from the patient to provide his/her contact information to the study team so a research assistant may contact them to discuss this research further or will provide an IRB-approved recruitment flyer to the patient Providers will be instructed to utilize HIPAA-compliant means to relay contact information to the study team.

Direct recruitment and referrals may occur in UW Health Ear, Nose, and Throat clinics and other clinics where patients who may qualify for this research are routinely seen, the UW Health Middleton Physical Medicine and Rehabilitation clinics, the Neuro Outpatient Rehabilitation Clinic or the Yahara Clinic),

Justification of Direct Recruitment and Referrals: For persons who have already been identified in clinical care as having dizziness or balance disorders, participation in this research will not adversely affect their clinical care, rather it has the potential to enhance their care in the event any positive treatment effects occur. Clinic schedules will be reviewed by clinicians associated with the study team to determine if any patients may be potential participants. Recruiting participants without screening clinic schedules would increase the study costs related to advertisement and significantly prolong the recruitment period to twice or three-times as long.

METHODS: ASSIGNMENT OF INTERVENTIONS

Participant Screening:

Dr. Grove conducted a telephone screening of potential participants. Only those individuals who responded to a flier or recruitment email, or those who are identified within the context of clinical practice, as described in this protocol, will be contacted for screening. Up to 3 call to reach potential subjects by phone before discontinuing attempts to contact potential participants. No recruitment letters will be sent ot those who cannot be reached by phone. The contact information for those who do not respond to voice messages will be shredded upon the completion of the study. The specific language used for the telephone screening is scripted.

It is desirable to conduct a telephone screening in order to save potential participants time, travel, and travel-related expenses involved with coming to the research lab for the sole purpose of conducting a screening when their eligibility is uncertain. During the screening, the research assistant will first ask permission to provide more detailed information about this research; then, the research assistant will provide a detailed verbal description of what is being consented to prior to requesting oral consent. The telephone script includes yes/no and open-ended questions. During the screening, minimal personal and health-related information that is not of a stigmatizing nature will be collected in order to help determine if a person is potentially eligible to participate. Additional health-related questions will be asked to identify those participants who are eligible but may be prone to adverse events. Specifically, we will ask potential participants about the following: limitations in range of motion; pain; lower body weakness; history or neurological, vestibular, peripheral neuropathy and migraine conditions, panic/anxiety; claustrophobia; and history of falls.

Conducting a phone screening will also give potential participants an advance opportunity to learn more about this research and ask questions prior to participating in the formal consent process. Potential participants may also opt not to consent to conducting a telephone screening and instead may choose to schedule an appointment to conduct the screening and consent process. The same script will be used for telephone and in-person screening.

During the telephone screening, the following information to be collected directly into ICTR OnCore and/or ICTR REDCap as appropriate: name, preferred name, address, home phone number, mobile phone number, age, birthdate, gender, height, weight, past medical history, past surgical history, current medications, UW Health record number, and the answers to the telephone screening questionnaire. We will also gather primary care provider name, primary care provider phone number, primary care provider address, emergency contact name, and emergency contact phone number at the time of the telephone screening in order to be well-prepared to respond to any unanticipated medical events that may occur while the person is in the lab, even prior to signing written consent or being able to answer additional questions. Electronic files will be removed from ICTR REDCap and ICTR OnCore ten years following study completion.

Allocation:

This trial follows a non-randomized, parallel groups design.

Blinding (masking):

It is not possible to mask participants from this behavioral intervention. Also, given the scope of the project and size of the study team, it is not practical to mask the researchers either.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data Collection Methods:

Telephone Screening: During the telephone interview, Dr. Grove entered all demographic and screening data into these databases in data entry forms with fields that are programmed to only accept valid entries. These data will be verified with participants when they attend their first study visit.

Patient-reported Outcome Measures: Participants who consent to the use of email for study-related purposes will enter their own data for most patient-reported outcome measures via secure, direct links to the ICTR REDCap database that will be contained in emails that will be automatically sent by ICTR REDCap at the appropriate timepoints (Table 3). Data entry fields in ICTR OnCore and ICTR REDCap are programmed to only allow valid responses. Paper forms will be used at the appropriate time points for those subjects who do not consent to the use of email for study-related purposes.

Performance-based Outcome Measures: A data collection file will be created for each participant within the file structure of the KIINCE device, which is password protected and housed in a secure lab. Only the study team will have access to these files. The data file records the following information: participant ID, age, weight, overall height, height to deltoid process, height to axilla, height to greater trochanter, current date, current time, and all of the variables required to document performance during testing and training. These data will be uploaded to ICTR REDCap for further data management and analysis after the last participant completes the study. A copy of the data file will remain on the KIINCE device for up to 10 years. The study team will consult with Amanda K. Reese, (608) 262-2059, amanda.reese@wisc.edu and Dharvesh Naraine, (608) 262-1664, naraine@wisc.edu regarding storage of participant data on the KIINCE device and as needed for matters related to data storage and security.

Health Records:

Many questions that we are asking during the telephone screening are directly related to the potential participant's past medical history, past surgical history, medications, diagnoses, testing, and date of onset of symptoms. The screening is worded in such a way that allows the research team to ask follow-up questions. For example, screening questions 8 and 9 refer to medications. If the potential subject answers yes, then an appropriate follow up question from the screener is, "What medications do you take?" Additionally, certain questions refer to specific diagnoses. If the potential subject answers yes, then the logical questions that follow are, "What is your diagnosis? When did your symptoms start? How were you treated?" Depending on whether a patient has a surgical diagnosis or not, the screener might also ask, "What type of surgery did you have?" The REDCap database that we use to gather data has built in comment fields that allow us to record additional information as needed.

In anticipation that participants may not be able to provide accurate or complete information during the telephone screening process, we are requesting to access the Health Link records of participants these participants. Dr. Mark Pyle is a neurotologist and Dr. Grove is a board-certified specialist in neurological physical therapy who specializes in the management of persons with dizziness and balance disorders. Thus, these study team members have appropriate clinical access to Health Link. Only Dr. Pyle or Dr. Grove were tohad access health records and only the health records of patricipants who are unable to provide complete and accurate information to the study team will be accessed. The only information that will be collected from these health records will be information that directly pertains to answering the questions posed during the telephone screening process.

Health record numbers will be collected from participants at the time of written, informed consent. This information will be entered directly into the REDCap and OnCore databases.

Data Collection Forms:

Data collection forms were developed in ICTR REDCap.

Data Management:

Study Management: The ICTR OnCore platform will be used for overall study management. In addition, ICTR REDCap will be used to collect patient-reported outcome measures through the use of surveys, as well as performance-based outcomes through the use of standardized forms. The ICTR REDCap and ICTR OnCore systems are password protected and user's roles are defined to allow appropriate access. Dr. Grove had completed training in ICTR OnCore for protocol, financial, and study coordinators, as well as the requisite training for ICTR REDCap. Fields are programmed to ensure the validity of the data.

Statistical Methods:

Data Analysis: Standard demographic data will be collected. Age, gender, height, weight, and body mass index will be summarized with descriptive statistics. Inferential analyses are expected to be hypotheses generating. Our a-priori alpha level for all analyses is 0.05.

All data collected will be entered in a custom-built project in the UW-Madison ICTR REDCap database so that it can be securely transferred to the study biostatistician (ICTR BERD). All analyses will be conducted using "R" for statistical computing version 3.5 or higher. The study biostatistician (ICTR BERD) will provide an independent review of the data analysis.

The specific aims for this trial and related analyses are as follows:

Aim 1 Analyses: The overall scores for each verticality perception test will be analyzed for sensitivity and specificity, positive and negative predicative values, likelihood ratio, and the area under the ROC curve (AUC) for correctly identifying self-reported visually-induced dizziness(44).

Aim 2 Analysis: Euclidian distance analyses(45) will be used to compare IP curves of healthy and symptomatic persons to determine if these curves have diagnostic value for visually-induced dizziness.

Aim 3 Analyses: Standardized mean difference will be used to assess if the intervention resulted in reduced symptoms based on pre-post comparisons of the Visual Vertigo Analogue Scale total score. Standardized mean difference will also be used to assess if the intervention resulted in improved verticality perception based on an effect size of 0.5 for pre-post comparisons of the average scores for the Rod and Disk Test, our primary outcome. Euclidian distance analyses will be used to assess for changes in balance control based on pre-post comparisons of the IP curves measured during visual-vestibular conflict. We will determine what, if any, immediate and short-term treatment effects resulted from the training by analyzing the data collected immediately pre- and immediately post-training. We will assess for short-term retention of any treatment effects by comparing outcomes measures data collected immediately following training and one week later.

Missing Data: We will conduct sensitivity analysis of missing data and follow the intention to treat principle.

We also plan to assess for relationships between our various outcome measures. These analyses will involve determining correlations between each of the patient-reported outcomes and between the patient-reported and performance-based outcomes. These secondary analyses will also be considered hypothesis generating and will be conducted at an unadjusted significance level of 0.05.

Feasibility and Contingency Plans:

Our ongoing research at UW Health and UW Madison has enrolled more than the necessary numbers of subjects for this study. In the event of sluggish enrollment, recruitment will be expanded to additional clinics. In anticipation that some participants may not tolerate testing well, specific guidance regarding modifying the intervention will be provided. Should any system fail to collect data, the visit will be rescheduled, or an additional visit will be added if necessary, in keeping with the study timelines

outlined in this protocol. No additional reimbursement to participants related to rescheduling or adding a research visit. Institutional support will be sought immediately if any key study staff leave.

METHODS: MONITORING

Data Monitoring:

We believe that the study team is well-equipped to accomplish data and safety monitoring for these studies for several reasons. First, we believe the study team has the requisite training and experience in this type of research. Second, we do not intend to enroll, high-risk or special/vulnerable populations. Third, survival is not an outcome. Fourth, this research is a Efficacy and of short duration. Fifth, the proposed research involves an investigator held exempted IDE. We are also not under any obligation to use independent monitoring as a condition of sponsorship or funding. Thus, we intend to utilize self-monitoring procedures.

Interim Analysis:

No interim analyses will be performed.

Harms:

Risks: Non-clinical Setting:

Physical Interventions Performed Outside a Clinical Setting: Participants complete tests of orientation and balance while in a supported standing position. The goal of these tests is to align images with gravity. All participants will also undergo sensory re-weighting training. The purpose of this training is to refine the perception of gravity and learn how to orient and balance oneself based more on somatosensory rather than visual input.

Non-clinical Setting: Study visits take place at the UW-Madison Neuromuscular Coordination Laboratory.

Plan for Handling Medical Emergencies: We were to call 9-1-1 in the event of a medical emergency. Drs. Gruben and Grove were trained in CPR and one or both will be present for all study visits. Dr. Pyle will provide general medical oversight for the trial. This is consistent with how medical emergencies are handled at outpatient physical therapy clinics that do not have an advanced practice or physician provider on site.

Potential Psychosocial Risks: This study includes completing a telephone screening. The questionnaires and assessments used in this study are new but are like those that are common and currently in use in clinical practice. These activities are like and of no greater risk than activities of daily living or that would be encountered during a standard clinical examination. Positioning in the device is a mild version of what is experienced by patients in clinical tilt table or rotational chair testing. The sensory re-weighting training is similar treatment activities currently performed in the clinic in that it involves training of orientation and balance. None of these activities is expected to pose significant psychosocial risks; however, many patients with dizziness and/ falls also have symptoms of anxiety. Therefore, some participants could become anxious during testing and/or training.

Common Risks: Studies show these assessment and treatment techniques are safe, well-tolerated, and associated with relatively mild and infrequent adverse reactions(46-48). However, potential adverse events (AE) include vertigo (dizziness), nausea, vomiting, fear of falling, loss of balance, headache, joint pain, and muscle soreness. Dizziness is often associated with emotional distress, such as with fear of falling. Mild dizziness (self-reported intensity ≤ 3/10) lasting ≤ 15 minutes is an expected,

temporary reaction; thus, only prolonged dizziness (>15 minutes) and/or severe dizziness (self-reported intensity ≥ 7/10) will be reported as an AE. Imbalance is also expected with assessment. If a participant reports a prolonged (> 24 hours) of worsened symptoms, he/she will be advised to contact his/her primary care provider for guidance regarding managing symptoms and/or to discuss if continued participation in this research is advisable. Subjects could experience vasovagal syncope due to being relatively immobile in a standing posture for periods of time.

Serious Risks: Falls or any injury that occurs while performing tests or interventions will be reported as a serious adverse event (SAE).

Minimization of Risks:

The risk of vertigo, nausea, and vomiting will be minimized by:
1) stabilizing the participants in a comfortable harness,
2) limiting duration of exposure to visually provocative stimuli (<~5 s per trial),
3) verbally monitoring participant tolerance and comfort to the intervention,
4) pausing the study for a rest break or terminating the study if symptoms don't resolve, and
5) allowing the participant to sit down with elevated legs within or outside the device during requested rest periods.

The risk of injury due to loss of balance will be minimized by:
1) recruiting participants that are independently ambulatory in the community,
2) providing physical assistance and handles to aid in negotiating the one 6 inch step up onto the device and the one step forward into position, and
3) placing the participant in a full torso harness attached to an overhead frame that prevents them from moving downward more than a few inches or tipping more than 30 degrees.

The risk of anxiety will be minimized by:
1) providing physical assistance stepping onto the device,
2) reassuring the participant that the safety harness will prevent any possible injury if they were not able to support themselves, and
3) guiding the participant through relaxation techniques as appropriate.

The risk of headache, joint pain, and muscle soreness will be minimized by:
1) ensuring that the participant is comfortable at all times via frequent verbal contact,
2) designing the device to be comfortable for all shapes and sizes of participants,
3) moving the person between postures (vertical, leaned left, leaned right) every 10 trials (~ approximately every 30 seconds), and
4) taking seated rest breaks as needed.

The risk of vasovagal syncope is minimized by:
1) asking about history of vasovagal syncope and excluding participants with frequent history (> 1/month),
2) reminding participants to move their legs every 10 trials,
3) using fan to provide gentle air flow for cooling and fresh air,
4) changing posture every 10 trials, and
5) frequently asking participant if they need a rest break or need to terminate the study.

The general risk of being restrained within a device is minimized by:
1) system design that allows the participant to be fully removed from all harness attachments within 5 seconds.

If patients experience a worsening of their condition during this study, they will be directed to contact their primary care provider for guidance. Participants will also be encouraged to consult with their primary care provider or prescriber in order to address any concerns related to withholding p.r.n. medications.

There is also a blood pressure cuff and water available in the lab. Dr. Grove is a physical therapy clinician and is trained in CPR and BLS.

Justification of Risks: Study procedures are consistent with functional and environmental challenges participants face during normal activities of daily living. The information gained about a participant's dizziness and/or imbalance may help him/her overcome current functional limitations and activity restrictions. Risks of recommended withholding p.r.n. medications are no greater than those associated with self-withholding of these medications. By their nature, the p.r.n. medications in question for this research are not life sustaining.

Auditing: All SAE will be reported to the PI immediately. Participants who experience any AE and SAE will be encouraged to report these to their primary care physician. Participants experiencing these events were to be followed up and assessed by Dr. Grove or Dr. Gruben as needed. ICTR OnCore will be used to document all AE and SAE. All AE will be reviewed by the study team on an as needed basis. Decision making regarding all AE and SAE will be reported in ICTR OnCore.

Provisions to Address Unanticipated Problems or Complications: The PI and Dr. Grove conducted continuous monitoring for unanticipated problems, AEs, and SAEs during each study visit. The PI or Dr. Grove also inquired about possible AEs and SAEs that may have occurred between study visits by asking patients to report any symptoms or concerns that may arise between or after study visits. As directed in the consent forms, participants will be advised to call either Dr. Gruben or Dr. Grove if they have any questions or concerns about their participation in this research. Should a possible unanticipated problems, AE, or SAE be suspected, Dr. Grove will discuss the issue or event with Drs Pyle and Gruben who hold final decision-making authority. Health Sciences Institutional Review Board guidance for reporting unanticipated problems and adverse events will be followed. If an unanticipated problem, AE, or SAE necessitates follow up with a medical provider, participants will be given direction in accordance with the information in the consent forms.

Potential Benefits of Participating:

Potential Benefits to Participants: Based on prior research findings, we believe this intervention may be effective in reducing or eliminating visual-dependence in humans. Thus, participants may experience improvement in how they feel when they are exposed to visually-provocative situations and environments as a result of undergoing this intervention. There is no guarantee of a positive outcome to the intervention and individual outcomes may vary.

Potential Benefits to Society: Falls are a major public health concern worldwide. Dizziness is a significant risk factor for falls. In order to reduce falls and pre-empt their consequences, it is important to develop effective treatments for dizziness. These studies will provide data regarding the efficacy of a new treatment for visually-induced dizziness. If this new treatment proves to be efficacious, then these methods could undergo further study through a phase 1 trial. If subsequent research continues to support the effectiveness of this training, then these methods could be translated into clinical applications. Use of this training technique could result in reduced symptoms of dizziness and fewer recurrent falls at the individual level, and reduced impact of dizziness and falls on productivity in the workplace and costs associated with health care expenditures related to morbidity and mortality associated with falls. This work may also lead to the development of additional testing and treatment techniques for use with individuals with dizziness and impaired balance.

ETHICS AND DISSEMINATION

Research Ethics Approval:

Institutional Review Board (IRB) Approval and Ethical Considerations: These studies involve minimal risks to study participants. Approval for these studies will be obtained from a University of Wisconsin-Madison Institutional Review Board (IRB). All study staff will adhere to the ethical and clinical standards established by the Belmont Report, Common Rule, Good Clinical Practices, HIPAA, and HiTECH. We will obtain HIPAA authorization for each participant as part of the consent process. We intend to collect the following identifiers: names, addresses, birth dates, age, telephone numbers, and email addresses.

The Johns Hopkins University School of Medicine Institutional Review Board intends to cede oversight of Dr. Grove to UW-Madison.

Protocol Amendments:

Modifications of the study protocol or procedures will be reported as required by the IRB.

Special Considerations and Procedures:

The tools used in the above referenced studies do not currently constitute a medical device as defined by the FDA (Section 201(h) of the Food, Drug, and Cosmetic Act). As such, we submitted a change of protocol to the IRB to replace the previous request for a non-significant risk determination and remove the requirements to conduct this study under the abbreviated IDE requirements of 21 CFR 812.2(b)(1) (including the application of 21 CFR 50 and 56).

Special Populations:

We do not intend to enroll any high-risk, special, or vulnerable persons, such as children, pregnant women, or individuals with cognitive dysfunction.

Consent or Assent:

Alteration of Informed Consent:

We will request a waiver of written documentation for consent so that we may obtain oral consent for:

1. Retaining the notes taken during the telephone screening
2. Communicating via email for study-related purposes
3. Obtaining oral consent to collect questionnaire data prior to written consent
4. Obtaining oral consent to have participants withhold medications prior to written consent

Alteration in the consent process is requested so the study team may collect patient-reported outcome measures data prior to written informed consent. During a telephone screening for potential participants, we will obtain oral consent to retain the notes taken during the screening for up to 10 years for the purpose of inviting them to participate in future studies, withhold p.r.n. medications, complete questionnaires prior to the initial study visit, and communicate with them via email for study-related purposes, which includes sending emails that contain links to ICTR REDCap that will allow them to complete study-related questionnaires prior to their first study visit.

Justification of Altered Consent: This study involves completing a telephone screening, questionnaires, and participating in clinical assessments that are common and currently in use in clinical practice at UW Health. These activities are similar to and of no greater risk than activities of daily living or that would be encountered during a standard clinic examination. The procedures outlined herein increase the

feasibility of conducting this project (and future projects) by reducing the time and financial resources required. These procedures also reduce the time commitment required of participants which makes it more likely that participants will enroll in and complete the study. This waiver would not adversely affect the rights and welfare of subjects. Of note, UW Health and the Wisconsin Physical Therapy Practice Act require a signed informed consent form for all patients receiving physical therapy services to be completed at the time of initial evaluation.

During the phone screening, minimal personal and health-related information that is not of a stigmatizing nature will be collected in order to determine if a person is potentially eligible to participate. It is desirable to conduct a telephone screening in order to save potential participants travel and travel-related expenses involved with coming to Madison from a distance for the sole purpose of conducting a screening when their eligibility is uncertain. Conducting a phone screening will also give potential participants an advance opportunity to learn more about this research and ask questions prior to participating in the formal consent process. Potential participants may also opt not to consent to conducting a telephone screening and instead may choose to schedule an appointment to conduct the screening and consent process.

Description of the Altered Consent Process: Dr. Grove conducted all screenings and Dr. Grove conducted consent meetings with potential participants. When contacting individuals for the telephone screening, Dr. Grove asked permission to provide more detailed information about this research. Then, Dr. Grove provided a detailed verbal description of what is being consented to prior to requesting oral consent to conduct the telephone screening. This includes informing potential participants that they are consenting to allowing the study team to maintain the confidential personal and health information for up to 10 years for the sole purpose of using it to invite the individual to participate in future research conducted by members of this study team at the UW-Madison. See the telephone script for complete details.

Written Informed Consent: A copy of the informed consent document will be provided to potential participants prior to the informed consent meeting. Copies will either be handed to potential participants, e-mailed, or mailed to participants at their request. The current version of the IRB-approved consent/HIPAA forms will be stored in the Neuromuscular Coordination Laboratory and in ICTR OnCore. The PI is solely responsible for ensuring that the most up-to-date version of the consent form is stored at each location and that all outdated forms are destroyed as soon as a new version is approved by the IRB. All collaborating providers and staff will be instructed that only Dr. Grove and Dr. Gruben are approved to obtain written consent from potential participants. Any patient that is inadvertently consented by anyone else will be required to repeat the consent process with Dr. Grove prior to being enrolled in this research. Any such events will be reported to the IRB.

The informed consent meeting will occur prior to the start of the first research visit in a private area within the Neuromuscular Coordination Laboratory. Each potential participant will be given a chance to review the form and consider it in private, without the presence of study staff, prior to being asked if they are ready to consent to participation. Prior to requesting that potential participants complete the consent form, Dr. Grove discussed the research in detail and answer any questions that arise. Each consented participant will be reminded that s/he may withdraw from the study at any time, for any reason, without any impact on his/her ongoing care. Consent will be fully documented in ICTR OnCore.

Privacy and Confidentiality:

Telephone Screening: Telephone screenings was conducted by Dr. Grove in a private room. Dr. Grove verifed that the potential participant is also in a place where they feel comfortable talking at that time.

Scheduling: Scheduling of research appointments was done directly with Dr. Grove or the research assistant and visits will not appear in Health Link.

Study Visits: Access to the Neuromuscular Coordination Laboratory is restricted to faculty, staff, and students directly associated with the lab. Thus, contact with persons not directly associated with this study is limited. All performance-related outcomes procedures will be conducted in areas specifically designed for the purposes of collecting these types of data.

Sensitive Information: We are not collecting particularly sensitive or any stigmatizing information about participants. The personal information we collect is only that which is needed to contact the participant, his/her primary care provider, and his/her emergency contact. The health information we collect is only that which is required to verify that the individual meets the inclusion criteria.

Retention of Telephone Screening Data: With oral consent provided by potential participants, we intend to retain the information collected during the telephone screening process in order to use it to offer individuals opportunities to participate in additional research studies that will be conducted by the applicants over the next 10 years. This information will only be available to the study team. This information will be de-identified and stored in ICTR REDCap and ICTR OnCore at the conclusion of the study. Each participant will be assigned a unique code which will be utilized to re-identify the information for possible use in future studies. The identification codes will also be stored in ICTR REDCap and ICTR OnCore. This information is intended for internal use only. If at some point in the future the study team determines that it is appropriate to develop a research registry, we will submit a separate application to the IRB for consideration of such a project.

Patient-reported Outcome Measures: Most patient-reported outcome questionnaires will be completed on-line through a secure connection to ICTR REDCap, otherwise paper will be utilized. Paper forms will not contain any information that would identify the participant other than the unique, study ID number. These data will be transcribed into ICTR REDCap immediately following data collection. Any paper data collection forms will be stored in a locked cabinet located in a secured location in the Neuromuscular Coordination Laboratory, University of Wisconsin-Madison. Digital records in ICTR REDCap and ICTR OnCore are password protected and clearance is associated with specific roles. Participants will be indirectly identified in research records through a unique participant identifier. All data will be coded and the link for coded data will be stored in ICTR REDCap and ICTR OnCore. Paper files will be shredded once data analysis is finalized. All identifiable subject information will remain stored in ICTR REDCap and ICTR OnCore. These files will be removed/deleted 10 years following completion of this research. The study team will consult with Amanda K. Reese, (608) 262-2059, amanda.reese@wisc.edu and Dharvesh Naraine, (608) 262-1664, naraine@wisc.edu regarding storage of participant data and will re-contact them as needed.

Performance-based Outcome Measures: These data will be collected on the KIINCE device and uploaded to ICTR REDCap for further data management, analysis and storage. The retention policy and procedures are the same as for the patient-reported outcome measures.

Competing Interests:

The PI is owner of a corporation, KIINCE LLC, set up to commercialize rehabilitation devices. That corporation currently has no financial value, no financial activity, and has not licensed any technology. The PI, through WARF, holds issued and pending patents related to the KIINCE device used in this study. No commercial interest holds any licensing agreements with WARF related to the device used in this study. The PI has an active Conflict of Interest management plan. Section VI. Human Subject Research of that management plan states: “For any human subjects protocol in which the entity a) sponsors the study, or b) owns or licenses a technology used in the study, the following rules apply. ...” As the entity neither sponsors the study nor owns or licenses a technology used in the study, the rules listed therein do not apply. An opinion supporting this conclusion has been provided by Stephanie Leroy, JD (attached to ARROW application)

Access to Data:

Only the study team will have access to the dataset. The study team is comprised of Drs. Gruben, Rosenberg, Pyle, Heiderscheit, Whitney, and Grove. Only Drs. Gruben and Grove will have access to the data key linking data to individual subjects. Dr. Whitney will only have access to summarized data in forms such as tables, graphs, and figures to be used on manuscripts and/or presentations. Dr. Whitney and Dr. Grove have been advised to consult their own institutions about the need for IRB oversight for her involvement in the study and confirm that she will not engage in human subjects research activities without prior IRB approval.

Ancillary and Post-trial Care:

If a participant is injured or gets sick because of this study, medical care will be available to them through UW Health, their local provider, or emergency services. In cases of an emergency, a member of the study team or the participant will call 9-1-1 or may be directed to go to the emergency room. For non-emergency medical problems, participants will be directed to contact their regular health care provider. Participants will be instructed to contact Dr. Kreg Gruben, at 608-262-2711 to report any sickness or injury associated with the study.

Timeline for Study Completion:

Pre-award Month 1	Protocol refinement Finalize Statistical Analysis Plan with BERD Human Subjects application development
Pre-award Month 2	Human Subjects approvals UW-SMPH review
Pre-award Month 3	REDCap data management project development, testing, and implementation OnCore trial management project development, testing, and implementation
Pre-award Month 4	ClinicalTrials.gov registration NCATS Prior Approval Submission NIH Human Subjects Registration Protocol manual development Regulatory binder development
Pre-award Month 5	Research Assistant hiring Confirm and test methods OnCore trial management project development, testing, and implementation
Post-award Month 1	Open study First subject enrolled
Post-award Month 3	Quarterly post-award reporting
Post-award Month 6	Quarterly post-award reporting
Post-award Month 8	Dissemination activities begin
Post-award Month 9	Quarterly post-award reporting
Post-award Month 10	Last subject completes the intervention Data analysis begins
Post-award Month 12	Close study Quarterly post-award reporting
Post-award Month 14	Report project accomplishments

Dissemination Policy:

The methods developed in the project will be disseminated at international research conferences aimed at both clinicians and researchers. Specifically, presentations will be made at the Society for Neuroscience Annual Meeting, Barany Society Meeting, and the Combined Sections Meeting of the American Physical Therapy Association over the next 3 years. Peer-reviewed research publications will be forthcoming.

We anticipate the analysis of data collected during this trial will drive iterative development related to the testing and treatment methods outlined here. The potential of this project to contribute to human health is the development of a novel methodology to improve human postural control and thus reduce fall risk for anyone with imbalance. Additionally, further refinement of the software control system, virtual environment stimuli, and hardware are needed before we pursue patenting, commercialization, and translation of these methods into clinical practice.

Authorship Guidelines:

The PI and Co-Is will be eligible for authorship. The methods/protocol and main trial publications will be authored as: Grove, CR, Rosenberg, A, Whitney, SL, Heiderscheit, BC, Pyle, GM, and Gruben, KG.

Reporting Guidelines:

The following protocol development and reporting guidelines were followed during the development of this non-randomized, Efficacy trial protocol for a non-pharmacological intervention.

CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials(49)

CONSORT 2010 Extension for Randomised Pilot and Feasibility Trials(50)

CONSORT 2010 Extension for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts(51)

CONSORT 2010 Extension for Better Reporting of Interventions: Template for Intervention Description and Replication TIDieR Checklist and Guide(52)

Public Access:

At present, there are no plans for granting public access to the full protocol, participant-level dataset, and statistical code.

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