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TITLE: INVENT VPT Trial: Incremental Velocity Error as a New Treatment in Vestibular Rehabilitation

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CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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14. ABSTRACT The purpose of this clinical trial is to compare traditional measures of vestibular rehabilitation (VPT) against a novel device (IVE) developed by the PI (Schubert) that has been shown to improve vestibulo-ocular reflex (VOR) function. We will examine critical dosing related questions in delivering vestibular rehabilitation for active duty service members with mild traumatic brain injury and civilians with vestibular hypofunction – both of which will be treated for rehabilitation given symptoms related to having a vestibular disorder. Data collection has started, all IRB approvals have been secured although amendments are pending. A manuscript describing the protocol has been accepted for publication.					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	5
5. Changes/Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	7
8. Special Reporting Requirements	9
9. Appendices	9

Introduction

The objective for this study is to compare traditional measures of vestibular rehabilitation (VPT) against a novel device (IVE) developed by the PI (Schubert) that has been shown to improve the vestibulo-ocular reflex (VOR) function. The goal is to examine and improve the current standard of care, while addressing critical dosing related questions in delivering vestibular rehabilitation. The study involves two patient cohorts and is designed to improve the vestibular-related symptoms and impairments associated with mild traumatic brain injury in active duty service members and in civilians with damage to their vestibular system. We will use a clinical trial cross-over design with randomization to either the control (VPT) or experimental (IVE) group and measure VOR function as well as subjective and functional outcomes in order to investigate the best means to improve delivery of vestibular rehabilitation. The cross-over design ensures each subject participates in each group.

Keywords

Vestibular rehabilitation; vestibulo-ocular reflex; gaze stability; balance exercises; traumatic brain injury; dizziness; imbalance; visual acuity

Accomplishments

The major goals of the project as approved by the SOW are:

Aim I. To compare gaze and gait stability outcome measures between a novel (incremental velocity error, IVE) and standard of care vestibular rehabilitation (VPT) intervention.

Aim II. To compare the unique effect of gaze stability training only (delivered via IVE or VPT) on posture and gait outcome measures

Aim III. Investigate the optimal frequency of gaze stability exercises taking into account burden on the patient and current best evidence.

Aim IV. Characterize inter-trial correlations in mTBI and civilians with UVH, predicting that individuals with mTBI will have higher inter-trial correlation and therefore less predictive ability than both healthy controls and civilians with UVH.

This grant design has 4 Major Tasks, each with a subtask listed here:

- Major Task 1: Establish two modes of gaze stability training (IVE and VPT)
Subtask 1: Prepare Regulatory Documents and Research Protocol for Study 1
- Major Task 2: Coordinate Study Staff for Clinical Trial
Subtask 1: Hiring and Training of Study Staff
- Major Task 3: Randomized Controlled Trial, Study
Subtask 1: Conduct Study, Report Findings
- Major Task 4: Clinical Trial Maintenance
Subtask 1: Coordinate with Sites & Data Core for monitoring data collection rates and data quality

Major Task 1: At the completion of year 3, we have completed each subtask related to protocol refinement, device and study regulatory documentation, and subject protection (IRB). During year 2, the PI designation was reassigned to Dr Bryan Ward, MD away from Dr Schubert – which took roughly eight months to resolve and now complete.

Major Task 1 is complete.

Major Task 2: At the completion of year 3, the JHU data collection site has completed all related training and hiring. For the Fort Belvoir (FBCH) data collection site, we budgeted the hiring of two part-time positions; physical therapist and research audiologist. We have secured a physical therapist to deliver both treatment arms, and she recently accomplished the appropriate clearances that had been delayed 3 months longer than typical given the pandemic. After 6 months, our PT is hired! The physical therapist will begin training for INVENT on November 8, which we believe will require 1 month of preparation prior to subject recruitment. Unfortunately, the research audiologist position was recently vacated 2 weeks ago when the person we had identified (and credentialed at FBCH) was forced to increase her effort on a pre-existing project given that projects' loss of someone related to a pandemic-created hiring freeze. In summary, the JHU site has completed each of the 8 specific subtasks related to this 2nd Major Task. However, at FBCH, two remaining subtasks exist

(hire and train the research audiologist). The FBCH Site PI (Stephanie Beauregard) and WRNMMC PI (Douglas Brungart) are aware of the urgency in hiring this 2nd part time person.

Major Task 2 is thus 100% complete at JHU, and 75% complete at FBCH.

Major Task 3: At the completion of year 3, we have begun data collection at the JHU site. To date, we have recruited 2 subjects. One of the subjects consented but failed the screening. The 2nd subject is currently in the washout phase for Aim 2. Given the three year delay we have experienced, we opted to conduct Aim 2 1st followed by Aim 3, given their designs are less burdensome on the research subjects. We intend to complete both Aims 2 and 3 in 1 year. We recognize this is ambitious, but we have set goals to recruit 4 subjects per month at JHU in attempt to reach such a goal (n=48 total, Aim2 and Aim3). We are hopeful to collect Aim 1 data during the no cost extension year.

At the FBCH site, we remain hopeful that the current patient consensus of service members being treated for mild traumatic brain injury will similarly sustain the 4 subjects per month goal. WE have no reason to believe otherwise.

At the JHU site, Major Task 3 is thus 100% complete. At the FBCH site, we expect to be 6-8 weeks behind and expect to recruit subjects towards the end of 2021/beginning of 2022.

Major Task 4: The primary goal for Major Task 4 is trial maintenance, data analysis and data dissemination. Trial maintenance is ongoing, and we have had to edit the RedCAP cloud database for various reasons that were only visible once we started data collection. Thus, we remain vigilant regarding trial maintenance. Aside from the INVENT trial design and protocol paper being accepted for publication, we don't anticipate much data analysis and publication to occur in the next year. If we can meet our n=48 subjects recruited in 1 year, then we will analyze the 2nd Aim data with expectation for publishing relevant findings.

Major Task 4 is ongoing for both JHU and FBCH sites

What opportunities for training and professional development has the project provided?

The INVENT project has led to the professional development of two post-doctoral fellows and two research physical therapists. The INVENT project design has trained these 4 personnel to navigate the redCAP database that had included creation of a data dictionary, writing basic code, and provided experience with data entry. In particular, one of the research physical therapists was inspired to write her own IRB protocol and was appointment a faculty title of Assistant Professor.

How were the results disseminated to communities of interest?

We have disseminated the INVENT protocol to the journal Trials, which has our paper in final revision.

What do you plan to do during the next reporting period to accomplish the goals?

We intend to work hard to reach the recruitment goals mentioned above and complete two Aims (Aims 2 and 3) in the next year. As able, we plan to write up any relevant findings.

Impact

What was the impact on the development of the principal discipline(s) of the project?

Too early to tell, but the potential impact will be to provide dosing amount in the prescription of gaze stability exercises for providers of vestibular rehabilitation

What was the impact on other disciplines?

To date, we have shown that the VOR gain (eye velocity/head velocity) is stable over time (Mahfuz et al 2020). This helps the clinician to have confidence that any change in VOR gain is related to the therapies attempting to change the gain and not variability in performance of the VOR.

What was the impact on technology transfer?

The primary outcome measure we collect is VOR gain (eye velocity/head velocity, normally 1), which is collected using the video head impulse test (vHIT). Currently, we are using off-the-shelf vHIT equipment to collect this outcome variable, but the method can be painful given how the goggles fit on the subject's face. With the assistance of co-investigator Americo Migliaccio, we are developing our own vHIT that is more comfortable to wear. This device is patent protected from our prior effort (pre-INVENT), and we intend to incorporate its use in the INVENT trial once we validate it.

Changes/Problems

Actual or anticipated problems or delays and actions or plans to resolve them

Delays from the pandemic and the unforeseen change in the JHU IRB Conflict of Interest policy have taken most of three years to resolve. The research administration from JHU followed the mandate specified by the NIH COVID-19 policy 'Flexibilities for Grant Recipients', to ensure salaries were continued to be spent from grants. However, I was able to shield some funding for two individuals that were able to have salary covered via other means. All personnel have been restored to original effort allocation.

In order to maximize our ability to complete the 3 data collection aims (4th aim is analytic), we will first collect the 2nd and 3rd Aims given their reduced time to complete. If we have time remaining in the study, and if we have enough salary support we will then collect Aim 1 during the No Cost Extension year (Sept 2022 – Aug 2023)

Changes that had a significant impact on expenditures

No more that has not already been reported.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None to report. This study does not use animals or biohazardous material.

Products

Journal publications. We have published the following studies related to the INVENT effort:

1. Rinaudo CN, Schubert MC, Figtree WVC, Todd CJ, Migliaccio AA. [Human vestibulo-ocular reflex adaptation is frequency selective](#). J Neurophysiol. 2019 Sep 1;122(3):984-993. doi: 10.1152/jn.00162.2019. Epub 2019 Jul 24. PMID:31339801
2. Schubert MC, Migliaccio AA. [New advances regarding adaptation of the vestibulo-ocular reflex](#). J Neurophysiol. 2019 Aug 1;122(2):644-658. doi: 10.1152/jn.00729.2018. Epub 2019 Jun 19. PMID: 31215309
3. Mahfuz M, Millar J, Schubert MC. [Repeated video head impulse testing in patients is a stable measure of the passive vestibulo-ocular reflex](#). J Otol. 2021 Jul;16(3):128-137.
4. Ervin AM, Schubert MC, Migliaccio AA, Perin J, Coulibaly H, Millar JL, Roberts D, Shelhamer M, Beauregard S, Pinto R, Brungart D, Ward BK. Incremental Velocity Error as a New Treatment in Vestibular Rehabilitation (INVENT VPT Trial): study protocol for a randomized controlled crossover trial. Trials Journal. In Press

No other books, non-periodical, one-time publications, conference papers, or other products have been presented.

Participants & other collaborating organizations

What individuals have worked on the project?

Name:	<i>Michael Schubert</i>
Project Role:	Hopkins site PI
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0002-5975-374X
% Effort:	40
Contribution to Project:	<i>Overall project management. Submittal of IRB, FDA paperwork, running lab meetings, etc....</i>

Name:	<i>Ann Ervin</i>
Project Role:	Co-I JHU
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0002-8610-4403
% Effort:	15 (restored)
Contribution to Project:	Assist with developing all of the training manuals and certification of training. She is the clinical trials expert for the study

Name:	<i>Colin Grove</i>
Project Role:	Post-Doctoral Fellow JHU
Researcher Identifier (e.g. ORCID ID):	ORCID ID: 0000-0001-7102-6708
% Effort:	100
Contribution to Project:	Assist with all aspect of the clinical trial. Ensure proper data collection at the FBCH site. Ensure FBCH is trained and all data appropriately uploaded from FBCH

Name	<i>Jennifer Millar</i>
Project Role:	PT JHU
Researcher Identifier (e.g. ORCID ID):	
% Effort:	40 (restored)
Contribution to Project:	JHU (civilian) site trial coordinator that is delivering the treatment arms and assisting with database entry

Name	<i>Jamie Perrin</i>
Project Role:	Statistician JHU
Researcher Identifier (e.g. ORCID ID):	
% Effort:	5
Contribution to Project:	Data analysis

Name	<i>Mark Shelhamer</i>
Project Role:	Co-I JHU
Researcher Identifier (e.g. ORCID ID):	
% Effort:	10
Contribution to Project:	Data analysis

Name	<i>Stephanie Beauregard</i>
Project Role:	Co-I FBCH
Researcher Identifier (e.g. ORCID ID):	
% Effort:	No Effort

Contribution to Project:	Site PI that is the clinical manager of the FBCH rehabilitation clinic.
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Name	<i>Douglas Brungart</i>
8 Project Role:	<i>Co-I WRNMMC</i>
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0002-0163-2734
% Effort:	No Effort

Name	<i>Stacy Pepitone</i>
8 Project Role:	PT FBCH (new hire)
Researcher Identifier (e.g. ORCID ID):	
% Effort:	50%
Contribution to Project:	Deliver the treatment arms at FBCH

Name	<i>Hamadou Coulibaby</i>
8 Project Role:	JHU RedCAP database creation
Researcher Identifier (e.g. ORCID ID):	
% Effort:	5%
Contribution to Project:	Assist data entry, database creation and management

Name	<i>Robin Pinto</i>
8 Project Role:	Research Audiologist FBCH
Researcher Identifier (e.g. ORCID ID):	
% Effort:	No Effort
Contribution to Project:	Consult on data collection of vestibular function test at FBCH

Name	<i>TBD</i>
8 Project Role:	Research audiologist
Researcher Identifier (e.g. ORCID ID):	
% Effort:	50%
Contribution to Project:	Conduct the outcomes measures at FBCH

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

"Nothing to Report."

What other organizations were involved as partners?

Fort Belvoir Community Hospital (FBCH), Walter Reed National Medical Military Center (WRNMMC), and the Neurological Research Institute of Australia (NeuRA) are also partners.

FBCH located in Fort Belvoir VA. FBCH provides access to the active duty service member patient population and the audio-vestibular function testing for the service members. We will use the FBCH facilities to collect data, and FBCH is providing In-kind support of related equipment to capture relevant outcomes data.

WRNMMC is in Bethesda MD and will provide audiological expertise in interpreting the laboratory testing results. Additionally, WRNMMC has the budget to fund the 50% effort of a PT and 50% effort of a research audiologist/research tech for this clinical trial. No data will be collected at WRNMMC.

NeuRA is in Sydney Australia and the location of the co-developer of the device being used as the experimental condition for this clinical trial. The Co-I associated with NeuRA has built the devices for the trial, from monies awarded for the trial. No data will be collected at NeuRA.

Special Reporting Requirements

COLLABORATIVE AWARDS: Not Applicable

Quad Chart

INVENT VPT Trial: Incremental Velocity Error as a New Treatment in Vestibular Rehabilitation
 PT170081 Psychological Health/Traumatic Brain Injury Research Program Complex Traumatic Brain Injury
 Rehabilitation Research Clinical Trial Award (W81XWH-I7-CTRR-CTA)



PI: Michael Schubert

Org: Johns Hopkins University

Award Amount: 2.5M

Study/Product Aim(s)

AIM I. To compare gaze and gait stability outcome measures between a novel (incremental velocity error, IVE) and standard of care vestibular rehabilitation (VPT) intervention.
Aim II. To compare the unique effect of gaze stability training only (delivered via IVE or VPT) on posture and gait outcome measures.
Aim III. Investigate the optimal frequency of gaze stability exercises taking into account burden on the patient and current best evidence.
Aim IV. Characterize inter-trial correlations in mTBI and civilians with UVH, predicting that individuals with mTBI will have higher inter-trial correlation and therefore less predictive ability than both healthy controls and civilians with UVH. This Aim involves no additional data collection.

Approach

This is a clinical trial comparing functional, physiological, and subjective outcomes between a novel device validated to improve the gain of the vestibulo-ocular reflex (VOR) and traditional methods of vestibular rehabilitation. Participants include active duty service members with dizziness and imbalance due to mild traumatic brain injury, and civilians with unilateral vestibular nerve hypofunction (typically due to viral assault or disease).



Left panel shows the traditional VOR exercise where subjects view a target (typically a letter) while moving their head left to right. Middle panel shows the StableEyes rehabilitation device and related touch screen controls (US Patent #9782068). Right panel displays VOR gain (eye/head velocity) normalized after StableEyes rehabilitation for 15 minutes.

Activities (2021)	Q1	Q2	Q3	Q4
Complete IRB protocols	[Blue square]			
Complete FDA application	[Blue square]			
Refine data collection/design	[Blue square]			
Train/Hire staff	Hiring need at FBCH, JHU complete			
Begin data collection				[Blue square]

Updated: Oct 29, 2021_Annual report. **Blue square** represents % complete relative to size of the cell.

Goals/Milestones

2019

- IRB approved for each site (100%) **Complete**
- FDA classification of INVENT Trial (NSR) **Complete**
- Research design formalized (100%) **Complete**
- Research training completed (75%)
- Begin data collection (**JHU, expect 6 weeks for FBCH**)
- Initiate data analysis
- Consider abstract submission with early data

Comments/Challenges/Issues/Concerns

Time remaining to allow recruitment goals. Participation of civilians given the pandemic

Appendices

NA