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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

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13. SUPPLEMENTARY NOTES

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. To date, we have secured local IRB approval (Johns Hopkins) and are awaiting final HRPO approval to begin data collection. We have secured FDA classification as a non-significant risk study, have developed the procedures manual, and have all necessary equipment to begin.

15. SUBJECT TERMS
Vestibular rehabilitation; vestibulo-ocular reflex; gaze stability; balance exercises; traumatic brain injury

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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 examine improve 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 subjects 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.

For year 1, we listed 16 subtasks as a part of the Major Tasks 1 that specified (per the SOW), Prepare Regulatory Documents and Research Protocol for Study 1. A few of the 16 listed items are no longer appropriate/needed, the others have all been initiated and/or are near completion. Ten of these 16 are complete, and bolded below – with *comments* added.

Establish early monthly meeting
Coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTAs) submission *AS NEEDED*
Coordinate with Sites for nondisclosure agreements (NDAs). *AS NEEDED*
Time required for submission and exemption of an Investigational Device Exemption (IDE) application to the U.S. Food and Drug Administration
Refine eligibility criteria, exclusion criteria, screening protocol
Finalize consent form & human subjects protocol

Coordinate with Sites for IRB protocol submission
Coordinate with Sites for JHU IRB review
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)
Submit amendments, adverse events and protocol deviations as needed *AS NEEDED*
Coordinate with Sites for annual IRB report for continuing review *AS NEEDED*
Build IVE devices
Confirm vestibular testing protocol
Refine IVE and establish the VPT research protocols
Train JHU and FBCH in IVE and VPT research protocols *This has started, not yet complete*

For Major Task 1, we have achieved 1.5 of three Milestones:

1. FDA approval of the IVE as a Non-Significant Risk study
2. Johns Hopkins IRB approval for the study.
    a. This approved JHU protocol has been submitted to HRPO and currently under review.

We are still awaiting HRPO approval which will complete the Major Task 1.

For year 1, we listed 7 subtasks as a part of the Major Tasks 2 that specified (per the SOW), Coordinate Study Staff for Clinical Trial. The major responsibility include hiring and training staff and developing a procedure's manual to ensure consistent delivery of the protocol. We are unable to hire staff until HRPO approval, though we have a majority of staff already in place. We have developed the procedure manual, and now are developing the certification procedures to ensure competent delivery of the protocol. Of the 7 specified items, only 1 is complete (training manual), all others related to hiring and training study staff.

For year 1, we listed two final Major Tasks (Task 3 - Randomized Controlled Trial, Study; Task 4 - Clinical Trial Maintenance**)**. No work has been completed as these are specifically related to data collection which we intend to start in 2020.

- **What opportunities for training and professional development has the project provided?**
    - *"Nothing to Report."*
- **How were the results disseminated to communities of interest?**
    - *"Nothing to Report."*
- **What do you plan to do during the next reporting period to accomplish the goals?**
    - The next major accomplishment is to obtain HRPO approval, which would enable the study to enroll patients.

Impact

- **What was the impact on the development of the principal discipline(s) of the project?**
    - As we refined and established the training protocols and the outcome measures, we realized that one of our secondary outcome measures (dynamic visual acuity) would best be tested using an impulsive (single) head rotation to the right or left. This is different than prior literature that has captured DVA using sinusoidal (back and forth) head rotation. As a result, we have initiated normative data collection to determine active impulse DVA scores in healthy controls. The value of this change in DVA testing is that it provides a more valid and functional assessment of how clearly we see during motion of our head during a manner that better reflects daily life.
- **What was the impact on other disciplines?**

- The impact of this change may be broad given rehabilitation providers would have a new method to treating (gaze stability exercises) and a new method of testing using impulse rotation (not sinusoid).

- **What was the impact on technology transfer?**
  - Dynamic visual acuity is already a well-known clinical measure of gaze stability during head motion. Therefore, there is no new technology to report.

Changes/Problems

We have no changes to report and are still on task as approved per the SOW and JHU IRB protocol.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - I anticipate finding and hiring a physical therapist (PT) at the Ft Belvoir Community Hospital may prove challenging once our currently appointed PT leaves (June 2020). We will start to advertise in the Spring of 2020 in attempt to ensure we have someone to take over.

- **Changes that had a significant impact on expenditures**
  - None to report

- **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 2 accepted publications with acknowledgement of Federal support from this current award. One of the MS (#2 below) is a review article of our work to date using the IVE method of which the current award is based. These both are included in the Appendix.

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

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:	*Michael Schubert*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0002-5975-374X

Nearest person month worked:	*4.8*
Contribution to Project:	*Overall project management. Submittal of IRB, FDA paperwork, running lab meetings, etc….*
Funding Support:	

Name:	*Jennifer Millar*
Project Role:	*PT*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4.8*
Contribution to Project:	*JHU (civilian) site trial coordinator that will deliver the rehab care and manage the RedCAP database*
Funding Support:	

Name:	*TBN*
Project Role:	*Post Doctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
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*
Funding Support:	

Name:	*Ann Ervin*
Project Role:	Co-I
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2.4*
Contribution to	*Assist with developing all of the training manuals and certification of*

Project:	*training. She is the clinical trials expert for the study*
Funding Support:	

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." However, we have not yet hired the Physical Therapist (PT) for the FBCH site given lacking HRPO approval. Fortunately, we have identified a PT already treating at FBCH that is eager to join our study. Per below, WRNMMC has the budget allocation to pay for this PT position.

- **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 will provide the active duty service member patient population as well as auditory and vestibular function testing. 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 located in Bethesda MD and will provide audiological expertise in interpreting the laboratory testing results. Additionally WRNMMC has the budget to fund 50% effort of a PT and an audiologist for this clinical trial. These positions have not been paid given lack of HRPO approval.

  NeuRA is located in Sydney Australia and the location of the co-developer of the device being used as the experimental condition for this clinical trial. He has built the IVE units for the trial, from monies awarded for the trial.

Special reporting requirements

- **COLLABORATIVE AWARDS:** Not Applicable
- **QUAD CHART**

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

PTI7008I Psychological Health/Traumatic Brain Injury Research Program Complex Traumatic Brain Injury Rehabilitation Research Clinical Trial Award (W8lXWH-l7-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).

Activities (2019)	Q1	Q2	Q3	Q4
Complete IRB protocols				
Complete FDA application				
Refine data collection/design				
Train/Hire staff				
Begin data collection				

Updated: Nov 8, 2019 Annual report. **Blue square** represents % completion relative to size of the cell.

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.

Goals/Milestones

2019

☐IRB approved for each site (75%)

X FDA classification of INVENT Trial (NSR) **Complete**

☐Research design formalized (95%)

☐Research training completed (75%)

☐Begin data collection

☐Initiate data analysis

☐Consider abstract submission with early data

Comments/Challenges/Issues/Concerns

N/A

Appendices

Attached are the two manuscripts acknowledging funding support.