

Award Number: W81XWH-19-1-0730

TITLE: Enriching Vitality and Compressing Risk for Alzheimer's Disease among Aging Veterans with TBI

PRINCIPAL INVESTIGATOR: Michelle Carlson, Ph.D.

CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

REPORT DATE: October 2021

TYPE OF REPORT: Annual

**PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012**

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REPORT DOCUMENTATION PAGE*Form Approved*
OMB No. 0704-0188

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1. REPORT DATE October 2021		2. REPORT TYPE Annual		3. DATES COVERED 01Sep2020 – 31Aug2021	
4. TITLE AND SUBTITLE Enriching Vitality and Compressing Risk for Alzheimer's Disease Among Aging Veterans with TBI				5a. CONTRACT NUMBER W81XWH-19-1-0730	
				5b. GRANT NUMBER AZ180131	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Carlson, Michelle M. E-Mail: mcarlo2@jhu.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) JOHNS HOPKINS UNIVERSITY 3400 N CHARLES ST BALTIMORE MD 21218-2608				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of this study is to evaluate the efficacy of a novel 3-D gaming intervention (Bandit the Dolphin) on executive functions (e.g., planning), mobility (e.g., walking) and in brain biomarkers linked to risk for Alzheimer's disease. This study will also assess if playing a game that trains to the real world will increase daily activities that in turn promote the brain and body. The scope is to conduct a 12-month randomized controlled trial of individuals with chronic or moderate TBI and evaluate cognitive, physical, psychiatric, physiological, and brain function at baseline, 3-month after the game intervention or healthy aging control arm, followed by a 9-month post intervention assessment. There is no data to report for this year due to delays caused by the pandemic and HRPO approval. The most substantial progress during this reporting period is an improved Bandit the Dolphin that enhances player enjoyment and standardizes in-game training, and replacement of the arm swimmer control to a health education program shown to benefit participants in published trials without affecting study outcomes.					
15. SUBJECT TERMS Traumatic brain injury, 3-D gaming interventions, Alzheimer's disease, dementia, mobility, neuroplasticity					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER (include area code)
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1. INTRODUCTION:

Those with past Traumatic Brain Injury (TBI) are at elevated risk for Alzheimer's disease and related dementias (ADRD), and the number of people who will become at risk for ADRD is estimated to triple to over 16 million by 2050. This highlights the need for developing novel interventions that target cognition and mobility to stop or slow the progression of the disease. Therefore, the purpose of this study is to evaluate the efficacy of a multimodal 3-D gaming intervention (Bandit the Dolphin) on executive functions (e.g., planning), mobility (e.g., walking) and in brain markers linked to risk for Alzheimer's disease. This study will also assess if playing a game that trains to the real world will increase daily activities that in turn promote the brain and body. The scope is to conduct a 12-month randomized controlled trial of individuals with chronic or moderate TBI. It will also measure cognitive, physical, psychiatric, physiological, and brain function at baseline after the 3-month game intervention or a health education control, followed by a 9-month post intervention assessment. We will utilize state-of-the-art computerized assessments, geospatial and neuroimaging technology.

2. KEYWORDS:

traumatic brain injury, exergame intervention, randomized control trial, Alzheimer's disease, dementia, cognition, mobility, neuroplasticity, brain biomarkers, functional neuroimaging, structural neuroimaging, life space, wearable technologies, lifestyle activities, well-being

3. ACCOMPLISHMENTS:

What were the major goals of the project?

- Major Task 1: Obtain IRB and USAMRMC approval for the study.
 - Sub task1: Received IRB approval from Johns Hopkins University (months 1-3, completed on 1/21/2020), Assembled a Data Safety Monitoring Board (DSMB) (months 1-3, completed on 11/27/2019).
 - Sub task 2: Regulatory review and approval by USAMRMC and HRPO (Approval notice 5/19/21)
- Major Task 2: Recruitment, Randomization, and Pre-Intervention (*delayed due to COVID-19*)
 - Subtask 1: In-clinic screening for eligibility, evaluate 5 participants from the clinic each month (months 7-18, ~3% completed). We have screened two patients for eligibility and identified 5 additional patients to be screened.
 - Subtask 2: Recruit and randomize eligible patients into experimental and active control group (months 7-18, ~1.5% completed). We screened, enrolled and conducted pre-intervention evaluations with one participant.
 - Subtask 3: Pre-intervention assessment (months 7-18, ~1.5% completed). We have conducted the pre-intervention assessments with one participant.
 - Subtask 4: Pre-intervention life space assessments using wearable technology for 1-2 weeks (months 7-18, ~1.5% completed). We have conducted the pre-intervention life space assessment with one participant.

- Subtask 5: Pre-intervention baseline brain imaging scans (months 7-18, 0% completed). We are awaiting approval by Johns Hopkins School of Medicine IRB for approval to change neuroimaging to the Kennedy Krieger Institute.
- Milestone #1: Co-author manuscript on using wearable sensors to assess activity and mood in patients with traumatic brain injury (TBI) (months 9-18, 0% completed) (*delayed due to COVID 19*).
- Major Task 3: Intervention (*delayed due to COVID-19*)
 - Subtask1: Have patients go through 3 months of gamer (experimental) or health education program (active control) arm (months 7-18, 0% completed)
- Major Task 4: Post-Intervention. (*delayed due to COVID-19*)
 - Subtask 1: Post-intervention assessments (months 11-23, 0% completed)
 - Subtask 2: Post-intervention wearable devices worn for 1-2 weeks (months 11-23, 0% completed)
 - Subtask 3: Post-intervention baseline brain imaging scans (months 11-23, 0% completed)
- Milestone #2: Co-author manuscript on effectiveness of study on cognitive function and activity in patients with TBI (pre-and post). (months 23-27, 0% completed)
- Major Task 5: Store and process imaging data.
 - Subtask 1: Store raw brain image scans on a secure computer for processing (months 23-25, 0% completed)
 - Subtask 2: Process brain image scans and derive key brain metrics (months 23-29, 0% completed)
- Milestone #3: Co-author manuscript on effectiveness of study using brain imaging data in patients with TBI (pre-and post), (months 24-32, 0% completed)
- Major Task 6: Evaluate patients at 12 months from baseline
 - Subtask 1: Active recruitment of participants again (months 19-30, 0% completed)
 - Subtask 2: Complete 12-month assessment (months 19-30, 0% completed)
 - Subtask 3: 12-month wearable devices worn for 1-2 weeks (months 19-30, 0% completed)
- Milestone #4: Co-author manuscript on quality of life of patients and caregivers pre and post study. (months 32-36, 0% completed)
- Milestone #5: Co-author manuscript on longitudinal effectiveness of study on cognitive function and activity in patients with TBI (baseline, 3-month and 12-month). (months 32-36, 0% completed)
- Milestone #6: Co-author manuscript on longitudinal effectiveness of study using brain imaging data in patients with TBI (baseline, 3-month and 12-month). (months 32-36, 0% completed)

What was accomplished under these goals?

Major activities:

During this reporting period, we improved Bandit the Dolphin with the KATA team. We changed our arm swimmer control arm to a Health Education program control which has greater benefit to participants without affecting study outcomes. We have been recruiting participants and enrolled, randomized and performed evaluations on our first participant. Please see below for greater detail.

Specific Objectives:

Intervention (Bandit): During this period, we finalized Bandit 2.0 with KATA, which now has built-in training features with an elaborate display to engage participants and increase user motivation, cognitive engagement, and visual enjoyment. We created a manual of operations to standardize training across levels. The performance metrics of game play have been upgraded to track rate of game learning and link study outcomes (e.g., cognition, life space activity, brain structure and function). We have a dedicated clinical space at the Johns Hopkins Bayview Campus for administering the intervention.

Active Control Arm: In piloting the arm swimmer control, we found that it was not well tolerated, and adopted a widely used and more enjoyable Health Education program control, shown to benefit participants in published intervention trials without affecting cognitive outcomes. The exposure to hours remain matched to the Bandit arm. The developer of this program, Dr. Nancy Glynn, is now a co-investigator. This new control will also optimize retention in the study, significantly reduce in-person contact and potential participant burden.

Assessments: We continued to test and refine the data analysis pipeline for the wearable devices. We have incorporated a state-of-the-art high-resolution scan to measure brain volume in subfields of the hippocampus that are specifically associated with memory and spatial navigation, which are targets of this intervention.

Recruitment of Participants: Dr. Peters and Ms. Richey connected with the Head Injury Outpatient Psychiatric Enhanced Services (HOPES) at Johns Hopkins School of Medicine to explain the study to facilitate recruitment. To increase the number of veterans recruited, Drs. Peters and Carlson have been working with recruitment sites including Walter Reed National Military Medical Center and the VA Maryland Research and Development. Recruiting from these sites and the Acquired Brain Injury Clinic and Memory and Alzheimer's Treatment Center at Johns Hopkins Bayview Medical Center maximizes our ability to recruit patients quickly.

Study Participants: Two participants have been screened in the clinic. One participant has completed the pre-intervention evaluations and has been scheduled for the intervention visits. Five additional patients have been identified to be screened in the clinic.

Research Staff: We hired, trained and certified four research assistants to conduct the intervention and assessments.

Significant results or key outcomes:

Nothing to report due to the COVID-19 pandemic.

Other achievements:

Nothing to report due to the COVID-19 pandemic.

Discussion of stated goals not met:

Several problems have contributed to stated goals not being met. The suspension of human subjects research at Johns Hopkins University through spring 2021 has contributed to significant delays. We have also experienced MRI Staffing issues due to the pandemic. Specifically, clinical

imaging staff have not returned or have taken higher paying positions outside Johns Hopkins University and positions have yet to be filled. To avoid delays, Dr. Carlson has negotiated with the Kennedy Krieger Institute’s FM Kirby Center to bring patients there. They are more expensive. There was a delay in final HRPO approval, which was granted in May 2021.

PROTOCOL (1 of 1 total):

Protocol [HRPO Assigned Number]: E00935.1a

Title: Enriching Vitality and Compressing Risk for Alzheimer’s Disease Among Aging Veterans with TBI

Target required for clinical significance: 66

Target approved for clinical significance: 66

Total subjects to date: 1

SUBMITTED TO AND APPROVED BY:

- Johns Hopkins Medicine Institutional Review Board (Protocol #IRB00218229)
 - IRB approval (IRB00218229) - 1/21/20
- USAMRMC HRPO
 - Pending approval

STATUS:

- (i) Number of subjects recruited/original planned target: 6/66
 Number of subjects screened/original planned target: 2/66
 Number of patients enrolled/original planned target: 1/66
 Number of patients completed/original planned target: 0/66

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:
 Amendment for the Active Control Arm.

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: Nothing to Report

Participant Status

HRPO Protocol Number	Protocol PI Name	Organization (Site)	Participants				
			Target (N)	Enrolled (N)	Completed (N)	Screened (N)	Other (N)
Pending	Michelle Carlson, Ph.D.	Johns Hopkins Bloomberg School of Public Health	66	1	0	2	0

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?

Quarter 1 (September 1, 2021-December 1, 2021)

- Recruitment, in-clinic screening, enrollment, randomization
- Pre-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Intervention and active control
- Data entry, cleaning, processing, and summary statistics

Quarter 2 (December 1, 2021 – March 1, 2022)

- Recruitment, in-clinic screening, enrollment, randomization
- Pre-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Intervention and active control
- Post-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Submit Johns Hopkins IRB continuing renewal
- Data entry, cleaning, processing, and summary statistics

Quarter 3 (March 1, 2022 – June 1, 2022)

- Recruitment, in-clinic screening, enrollment, randomization
- Pre-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Intervention and active control
- Post-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Data entry, cleaning, processing, and summary statistics

Quarter 4 (June 1, 2022 – September 1, 2022)

- Recruitment, in-clinic screening, enrollment, randomization
- Pre-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Intervention and active control
- Post-intervention: evaluations, activity monitoring with wearable devices, and brain imaging scans
- Data entry, cleaning, processing, and summary statistics
- Begin drafting: Co-author manuscript on using wearable sensors to assess activity and mood in patients with traumatic brain injury (TBI)

4. IMPACT:

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

The modifications to Bandit the Dolphin were designed to enhance player enjoyment and elicit greater effects on our outcomes, which will further strengthen the need for using novel gaming systems that train both cognitive and motor function simultaneously in patient populations at risk of cognitive and physical disability. The change in the control group from the arm swimmer to the Health Education program will provide a better comparison to Bandit as well. Making these improvements during this pilot trial is important to determine efficacy and power for a larger-scale, multi-site trial with longer-term follow-up of cognitive and brain health.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

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

Actual problems:

We have experienced several problems that has contributed to goals not being met. Suspension of human subjects research at Johns Hopkins University through spring 2021 has contributed to substantial delays. We have also experienced problems with MRI staffing due to the pandemic. Specifically, clinical imaging staff have not returned or have taken higher paying positions outside Johns Hopkins University and positions have yet to be filled. To avoid delays, Dr. Carlson has negotiated with the Kennedy Krieger Institute's FM Kirby Center to bring patients there. They are more expensive. There was a delay in final HRPO approval, which was granted in May 2021. Due to these delays we will seek a no-cost extension to the project.

Anticipated problems:

Given the delta variant of COVID-19, it is possible that Johns Hopkins University may limit on campus activities if there is an outbreak. All staff are required to be vaccinated and adhere to safety and cleaning protocols as outlined by Johns Hopkins University.

Changes that had a significant impact on expenditures

Due to Covid-19 restrictions, we have not been able perform aspects of the project that significantly affect expenditures. These include staff hours for conducting the evaluations and intervention, recruitment of research participants which requires remuneration for their participation, parking and travel costs, and inability to conduct neuroimaging sessions for which we would be invoiced.

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

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:**• Publications, conference papers, and presentations**

Nothing to Report

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

- **Website(s) or other Internet site(s)**

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Investigator	Project Role	ORCID	Percent Effort	Contribution to Project
Michelle Carlson, Ph.D.	Principal Investigator	0000-0003-2465-7421	10	Contributed to initial IRB approval and assembled DSMB. Led the work with KATA and research teams to refine Bandit the Dolphin intervention to optimize the cognitive and physical benefits. Worked with research group to finalize the intervention protocol. Led the development of the behavioral and activity monitoring assessments. Submitted quarterly reports, quad charts, and HRPO documents via eBRAP. Hired personnel. Trained and certified research assistants on evaluations and intervention with Dr. Eldreth. Led the justification for resuming human subjects research at JHU.
Matthew Peters, M.D.	Co-Principal Investigator	0000-0002-5668-4566	5	Contributed to initial IRB approval and assembled DSMB. Submitted IRB amendments and continuing review. Led the efforts to obtain approval by the Johns Hopkins IRB to resume in-person research. Presented to clinic where research will occur and got approval for a designated intervention space. Assisted with the finalization of questionnaires and reviewed data collection forms. Began recruiting, screening and enrolling patients.

Investigator	Project Role	ORCID	Percent Effort	Contribution to Project
John Krakauer, M.D.	Co-Investigator	0000-0002-4316-1846	5	Facilitated and guided co-investigators and the team in the implementation and adaptation of Bandit the Dolphin intervention.
Omar Ahmad, Ph.D.	Co-Investigator		5	Engineered the software development and lead the KATA team of computer scientists to incorporate the changes requested for Bandit the Dolphin by Dr. Carlson and her team.
Dana Eldreth, Ph.D.	Project Coordinator	0000-0002-8392-0077	20	Led the development of the evaluation protocol and training manuals along with Dr. Carlson. Orchestrated the finalization of the assessments, questionnaires, and data logs. Created the REDCap Project with assessments and data collection infrastructure. Led the efforts to evaluate and test revisions made to Bandit the Dolphin intervention with Dr. Carlson. Worked with Dr. Carlson to hire, train and certify research assistants on evaluations and interventions. Assisted with IRB submissions. Responsible for creating quarterly technical reports, quad charts, HRPO and other administrative details specific to the DoD. Organized regular meetings team to discuss the status of the project and Bandit 2.0 revisions. Evaluated participants.
Lisa Richey, B.S.	Research Coordinator	0000-0002-3822-1752	20	Led initial IRB drafting and approval. Led messaging to DSMB participants. Helped present to clinic where research will occur and got approval. Reviewed data collection forms. Leading the protocol development for the Johns Hopkins Bayview site. Provides input on questionnaires and insight into working with this patient population. Trained on evaluations and intervention.

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?

We have partnered with the University of Pittsburgh on the development and training for the Health Education Control. The developer of the program, Dr. Nancy Glynn, is now a co-investigator on the study.

- **Organization Name:** University of Pittsburgh
- **Location of Organization:** Pittsburgh, PA
- **Partner's contribution to the project**
 - **Financial support:** N/A

- **In-kind support:** N/A
- **Facilities:** N/A
- **Collaboration:** Dr. Glynn at the University of Pittsburgh developed the Health Education program that will be used as our control arm. Her staff will train our staff on administering this program to the control group.
- **Personnel exchanges:** N/A
- **Other:** N/A

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: Included

9. APPENDICES

Nothing to report.