

**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**

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**TYPE OF REPORT: Annual**

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| <b>6. AUTHOR(S)</b><br><br>Carlson, Michelle M.<br><br>E-Mail: mcarloso2@jhu.edu   |                         |                                 |   | <b>5d. PROJECT NUMBER</b>                         |   |
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| <b>13. SUPPLEMENTARY NOTES</b>   |                         |                                 |   |   |   |
| <b>14. ABSTRACT</b><br>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. |                         |                                 |   |   |   |
| <b>15. SUBJECT TERMS</b><br>Traumatic brain injury, 3-D gaming interventions, Alzheimer's disease, dementia, mobility, neuroplasticity   |                         |                                 |   |   |   |
| <b>16. SECURITY CLASSIFICATION OF:</b>   |                         |                                 | <b>17. LIMITATION OF ABSTRACT</b><br><br>UU | <b>18. NUMBER OF PAGES</b><br><br>13              | <b>19a. NAME OF RESPONSIBLE PERSON</b><br>USAMRDC |
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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
  - Subtask 1: In-clinic and community recruitment & screening for eligibility, evaluate 5 participants from the clinic each month (months 7-18, ~152% completed). We have screened approximately 100 patients for eligibility of which ten have enrolled. We have randomized a total of 10 participants into the experimental and control groups.
  - Subtask 2: Pre-intervention assessment (months 7-18, ~15% completed). We have conducted the pre-intervention assessments with 10 participants.
  - Subtask 3: Pre-intervention life space assessments using wearable technology for 1-2 weeks (months 7-18, ~9% completed). We have conducted the pre-intervention life space assessment with six participants.
- Subtask 5: Pre-intervention baseline brain imaging scans (months 7-18, 8% completed). We have completed five participants.
- 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).

- Major Task 3: Intervention
  - Subtask 1: Have patients go through 3 months of gamer (experimental) or health education program (active control) arm (months 7-18, 5% completed). We have two participants who successfully completed the gaming intervention and one participant who successfully completed the health education program. We currently have two additional participants who are more than halfway through completing the health education program. We also currently have one participant who is more than halfway through completing the gaming intervention.
- Major Task 4: Post-Intervention.
  - Subtask 1: Completed 3-month post-intervention assessments on three participants (months 11-23, 5% completed). We will complete the 9-month post-intervention on 2 participants in October.
  - Subtask 2: Completed post-intervention wearable devices on two participants (months 11-23, 3% completed). We will complete the 9-month post-intervention on 2 participants in October.
  - Subtask 3: Post-intervention baseline brain imaging scans (months 11-23, 0% completed). We will complete one 3-month post-intervention MRI in October.
- 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 and process raw data and complete data quality control (months 23-25, 8% completed).
  - Subtask 2: Derive key brain metrics (months 23-29, 8% 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 have been recruiting, enrolling, randomizing, administering evaluations, performing MRIs, and completing the Bandit intervention and Healthy Aging Program active control arm on our participants. Please see below for greater detail.

Specific Objectives:

*Intervention (Bandit):* We administered the Bandit intervention to one participant.

*Active Control Arm:* We administered the Healthy Aging Program to three participants and completed administering the Healthy Aging Program to one participant.

*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:* We began recruiting from additional resources such as the ADRC (Johns Hopkins Alzheimer's Disease Research Center) database.

*Study Participants:* 1) administered pre-intervention evaluations to one participant, (2) administered Bandit intervention to one participant, (3) administered Healthy Aging intervention to three participants, (4) completed administering Healthy Aging intervention to one participant, (5) conducted baseline MRI scans to two participants.

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

Significant results or key outcomes:

Nothing to report.

Other achievements:

Nothing to report.

Discussion of stated goals not met:

Recruitment has been an ongoing challenge, so we are developing new recruitment methods to meet our goals.

**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: 10

**SUBMITTED TO AND APPROVED BY:**

- Johns Hopkins Medicine Institutional Review Board (Protocol #IRB00218229)
  - IRB approval (IRB00218229) - 1/21/20
  - IRB Continuing Review 1 – approved: 12/9/2020

- IRB Continuing Review 2 – approved: 11/8/2021
- IRB Continuing Review 3 – approved: 9/21/2022
- USAMRMC HRPO
  - Approved – 5/19/21

**FOURTH QUARTER STATUS:**

- (i) Number of subjects recruited/original planned target: 89/66  
 Number of subjects screened/original planned target: 49/66  
 Number of patients enrolled/original planned target: 10/66  
 Number of patients completed/original planned target: 0/66

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:  
 JHU IRB amendments during this quarter:

- Approved amendment to add and remove study team members.
- Amendment under review to add study team member.

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

**Annual Enrollment Status To-Date**

| HRPO Protocol Number | Protocol PI Name        | Organization (Site)                             | Participants |              |                    |                    |              |           |
|----------------------|-------------------------|---|--------------|--------------|--------------------|--------------------|--------------|-----------|
|                      |                         |   | Target (N)   | Enrolled (N) | Completed 3-mo (N) | Completed 9-mo (N) | Screened (N) | Other (N) |
| Pending              | Michelle Carlson, Ph.D. | Johns Hopkins Bloomberg School of Public Health | 60           | 10           | 0                  | 0                  | 85           | 0         |

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

We have hired, trained, and certified three research assistants to aid in participant screening, pre & post intervention evaluation, and intervention (both Bandit & Healthy Aging control arm).

**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, 2022-December 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 2 (December 1, 2022 – March 1, 2023)***

- 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, 2023 – June 1, 2023)***

- 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, 2023 – September 1, 2023)***

- 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?**

We aim to determine the efficacy of a complex cognitive-motor game, Bandit the Dolphin, on cognition, brain function and structure, lifestyle, and independent activities of daily living in patients with past traumatic brain injury (TBI) in comparison to a health education control. WE aim to examine the influence of this intervention on biological markers that are predictive of Alzheimer’s disease and Alzheimer’s related dementias by collecting pre and post intervention brain imaging data. We aim to assess durability of any observed change in cognition, psychiatric

symptoms, mobility, and physical function 9-months post intervention. We plan 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:**

The most significant contributor to delays during this quarter is the recruitment of patients and Veterans. This is often due to the age range, time commitment of the intervention, time since TBI, and compensation for participation and travel. We are doing our best to address this by pursuing additional recruitment resources mentioned previously (i.e., ClinicalConnection, ResearchMatch, NeuroRestorative, Brain Injury Association of Maryland, Mary T. Maryland, JHU-ADRC, and media outlets) and changing our time since TBI from 3 to 2 years. We also created an amendment to change the inclusion criteria from mild to moderate TBI to mild, moderate or severe TBI.

**Anticipated problems:**

Given the challenge of recruitment, we anticipate needing to recruit from additional sources.

**Changes that had a significant impact on expenditures**

Given the challenge of recruitment, we have had to devote more resources and expenditures to recruitment efforts.

**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?

| <b>Investigator</b>     | <b>Project Role</b>       | <b>ORCID</b>        | <b>Percent Effort</b> | <b>Contribution to Project</b>  |
|-------------------------|---------------------------|---------------------|-----------------------|---|
| 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.  |
| 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 | 21                    | 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. |
| Karin Kartawira, B.S. | Research Assistant           |                     | 100% (hourly)                                      | Data collection, intervention.  |
| Gregory Wade, Ph.D.   | Research Program Coordinator | 0000-0003-4189-0997 | 7% (Dr. Bakker lab member started at 15% in March) | Neuroimaging data analysis  |
| Emily Richards, B.A.  | Research Coordinator         | 0000-0002-9150-513X | 40%  | Data collection, Intervention, Recruitment, Healthy Aging Program, Data processing  |

**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.