

AWARD NUMBER: W81XWH-16-1-0519

TITLE: Intensive Cardiorespiratory Exercise (ICE) to remediate mild traumatic brain injury in active duty service members

PRINCIPAL INVESTIGATOR: David Johnson

**RECIPIENT: University of Kansas
Lawrence KS 66045**

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

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14. ABSTRACT AEx is a well-documented pathway to health and resilience, especially in ADSM. Regular exercise induces positive physiologic and psychological benefits and prevents many of the same chronic illnesses that are linked to mTBI. Exercise has a biologically plausible and temporal relationship with coronary heart disease, atherosclerosis, stroke, type 2 diabetes, some cancers, and all-cause mortality. Three clinical evaluations will be conducted in TBI-R&R at baseline and 6-month follow up for brain MRI, psychological, and comprehensive physical fitness testing. To monitor safety, AEx dynamics, and adherence throughout the intervention, ADSM will perform monthly a standard US Army exercise challenge, the 2-mile run where we will monitor mood, and salivary cortisol in response to the AEx challenge. Depending on an ADSM's performance on the 2-mile run, the interventions prescription for heart rate, distance and duration goals will be increased in a controlled stepwise fashion to meet increasing CR fitness goals.					
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Three clinical evaluations will be conducted in TBI-R&R at baseline and 6-month follow up for brain MRI, psychological, and comprehensive physical fitness testing. To monitor safety, aerobic exercise dynamics, and adherence throughout the intervention, ADSM will perform monthly a standard US Army exercise challenge, the 2-mile run where we will monitor mood, and salivary cortisol in response to the aerobic exercise challenge.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

mild traumatic brain injury; Alzheimer's disease; trauma; cardiorespiratory fitness; psycho-social intervention

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Assess the efficacy of aerobic exercise (AEx) in ADSM with mTBI. We will enroll 100 ADSM from the 1st Infantry Division (1ID) with mTBI for a 6-month clinical trial examining the effect of ICE as an intervention. In this clinical trial, ADSM will be randomly assigned to either physical training enhanced with ICE (n=67) or usual physical training (uPT; i.e., mandatory morning exercise as part of their active duty assignment; n=33). Depending on an ADSM's performance on the AEx challenge, the intervention's prescription for heart rate, distance and duration goals will be increased in a controlled stepwise fashion to meet increasing CR fitness goals. AIM 1. Determine if ICE is associated with cognitive benefits in mTBI. We hypothesize that ICE will be associated with gains in Global Cognition (primary outcome) and Executive Function, Attention, and Visuospatial Processing abilities (secondary outcomes). AIM 2. Determine the effect of ICE on depressive symptoms in mTBI. We hypothesize that ICE will be associated with a reduction in depressive symptoms compared to uPT. AIM 3 (EXPLORATORY). Test potential mechanisms that may mediate or moderate how ICE affects cognition and depressive symptoms. Based on our prior work in older adults, we hypothesize that gains in CR fitness (VO₂peak) will mediate benefits in mTBI symptomatology (cognitive and depression symptom severity).

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1) *major activities* (CY16/17 Goals):

- Initiate ICE & Demonstrate Intervention's Safety
- Instrumentation and FITBIR Reporting Pathways Finalized
- ADSM recruitment
- Train patient navigators to conduct intervention, data collection, QA data review
- Implement ICE intervention in 1st Infantry Division

2) *specific objectives*:

- Coordination with IACH to hire personnel, identify space, purchase equipment, plan enrollment, and coordinate with IT.
- Coordinate with Sites for contractual agreements
- Local KU IRB Review
- HRPO IRB Review
- Coordinate with IACH for IRB protocol submission
- Refine eligibility criteria, exclusion criteria, screening protocol
- Consultation with the FITBIR team
- Verification of data elements for entry into FITBIR
- Finalize consent form & human subjects protocol Submit 5 revisions
- Advertise and interview for project related staff
- Coordinate for space allocation for new staff
- Coordinate with Sites for Independent Evaluators hiring and trainings
- Coordinate with Sites for training Independent Evaluators to max concordance
- Milestone Achieved: Research staff trained
- KU CRMDA to plan data workflow and schedules
- Finalize workflow and schedules jointly with IACH associated departments
- CRMDA to generate OCR forms in Colectica
- Coordinate with TBI-R&R for basic patient flow all study steps, data collection database requirements, and study coordinator action list
- TBI-R&R roles queried for enrollment
- Pt Navigator contacts division to start recruitment
- Evaluation participant profiles to determine if they are eligible for enroll in the study and eligible for randomization

3) *significant results or key outcomes*: Analyses not yet run. No outcomes to report.

4) *other achievements*: None.

5) *discussion of stated goals not yet met...* CY16/17 goals included:

- Recruitment of 60 ADSM
- Qualitative Analysis of Adverse Events and Adherence Data
- Publication of Preliminary Safety and Adherence Paper

Because the ICE intervention started late (August) initial recruitment has run into the Fall and Winter months and thus slowed. In part due to (1) our reluctance to have the critical phase of the AEx intervention (most aerobically intense) occur during the coldest months of the year and (2) the resistance of the ADSM to commit to cold weather running. By result we have 4 enrollees at the time of this report which prevents any qualitative or quantitative analysis of the data and writing manuscripts. Project was terminated due to lack of participation.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to Report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

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

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Nothing to Report

- 4. IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Working with division to meet the needs of the ADSM and their commanding officers has been challenging at times. Recruitment within an active duty military population has presented us with 3 primary impediments to enrollment: 1) We began the ICE study as two brigades stationed at Riley were in transition, 1st returning and 2nd deploying. This interfered with potential ADSM participants meeting the Inclusion Criteria (stable station to support the 6 months of participation). This also (understandably) focused 1st ID leadership on dominant transition concerns. Now that the 2nd Brigade has returned and scheduled vacations and De-mob finished, we have access to more stable ADSM population at Ft Riley. 2) A large fraction of individuals who have a documented history of mTBI frequently carry profiles prohibiting running. Even though these profiles are believed to be temporary, in practice the profiles are renewed up until the point the service-member is Med-boarded, indicating that these mild TBI diagnoses are severe enough to interfere with daily function. 3) Individuals with an undocumented history of mTBI resist reporting their history for fear of a negative impact to their military career or potential for advancement (regardless of reassurance of confidentiality). In spite of these setbacks, our recruitment team now understands the exigencies of this research population better than ever and we continue to find new ways to recruit and intensively exercise these ADSM. First and foremost, we are actively recruiting in 1st Brigade, now that most ADSM are back on base. Specifically we are raising 1st Brigade surgeon awareness of the mTBI criteria and meeting frontline health care providers to describe the study and inclusion criteria. It was determined that these challenges were insurmountable.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

- 5. CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Due to issues with recruitment, it was determined to terminate the project.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

See recruitment issues detailed in Question 3 - Goal 5 above.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Due to issues with recruitment, it was determined to terminate the project.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No changes have been made to original protocol approved in July.

Significant changes in use or care of vertebrate animals

Not applicable – animal research being conducted.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume; year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

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

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

Technologies or techniques

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report

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

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report

Other Products

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Database and processes created to optically character recognize handwritten paper form data to a csv file using many common clinical instruments available in FITBIR.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Name: **Paul Johnson**
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *1*
Contribution to Project: *Dr Paul Johnson has served as PI of record since August 1st, 2017 when Dr D. Johnson took a new faculty position at UC Davis.*

Name: **David K Johnson**
Project Role: *Co-Investigator (Former PI)*
Researcher Identifier (e.g. ORCID ID): *0000-0003-3670-8054*
Nearest person month worked: *3*
Contribution to Project: *Dr David Johnson supervises all aspects of the research trial including execution of the contract at all 3 sites (KU, IACH & UCDavis).*

Name: **Stafford Gosser**
Project Role: *Project Coordinator*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *8*
Contribution to Project: *Project coordinator recruits, tests, and runs ADSM participants.*

Name: **CPT Carly Cooper**
Project Role: *IACH Site PI*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *In Kind*
Contribution to Project: *Execution of the contract on site.*

Name: **Eric Vidoni**
Project Role: *Physical Therapist*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *1*
Contribution to Project: *Dr. Vidoni is an expert in conducting AEx interventions. He has been providing oversight of the project coordinator and advise to insure and enhance quality control.*

Name: **John Templin**
Project Role: *Statistician*
Researcher Identifier (e.g. ORCID ID): *None*
Nearest person month worked: *1*
Contribution to Project: *Dr. Templin is a quantitative psychologist with expertise in conducting clinical research. He has been advising the trial team re methodology and assessment database creation.*

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

The PI of record is now Professor Paul Johnson who has taken over for David Johnson. Dr Johnson transitioned to a new faculty position in the Dept of Neurology at UC Davis.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: N/A