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TITLE: The Prevalence of Alzheimer's Disease Pathology After Traumatic Brain Injury in Veterans and Civilians: A Biomarker Study of Beta-Amyloid and Tau

PRINCIPAL INVESTIGATOR: Christopher Rowe

CONTRACTING ORGANIZATION: University of Melbourne

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14. ABSTRACT

Background: Retrospective studies suggest that traumatic brain injury (TBI) increases the risk of Alzheimer’s disease (AD) four-fold. This has not been supported by recent PET imaging studies including our previous work (Doré V, Cummins TL, et al. Tau, β -amyloid, and glucose metabolism following service-related Traumatic Brain Injury in Vietnam war veterans: The AIBL-VETS study. **PREPRINT.** <https://www.medrxiv.org/content/10.1101/2022.03.10.22272230v1>). PET scanning to measure the proteins Amyloid and Tau are the key predictors of future AD. This study investigates civilians and veterans with single TBI using the latest generation of more sensitive imaging biomarkers.

Hypothesis: *That individuals with traumatic brain injury (TBI) have a higher prevalence of AD related pathology and neurodegeneration compared to age matched controls.*

Study Design: We will use the latest generation of PET imaging and 7 Tesla MRI to measure AD pathology and chronic traumatic brain damage. We will study 150 elderly TBI subjects and 100 age-matched controls. In addition, psychological testing will be carried out such that the imaging results can be tested for correlation with clinical endpoints.

Progress: The Covid-19 pandemic has delayed the 7T MRI imaging and recruitment of Vietnam veterans has been difficult. Never-the-less good progress has been made. To date 28 Vietnam war veterans with TBI, 19 veteran controls, 95 persons with moderate or severe TBI due to motor vehicle accident and 63 age matched MVA controls have been studied with amyloid and tau PET, 3T MRI and neuropsychological testing. Consequently overall recruitment is on schedule with 82% of TBI and 82% of control assessments complete at the end of year two except for 7T MRI. This is due to Covid lockdown of the 7T MRI facility but scanning has now commenced.

Results: Analysis to date shows **no increase in amyloid or tau** in veterans or motor vehicle accident victims with TBI compared to controls (manuscript currently under review). 7T MRI has commenced and all participants have re-consented for data sharing through FITBIR. Data upload has commenced to FITBIR.

Conclusion and Significance: Results to date suggest that TBI does not result in increased development of Alzheimer’s disease. 7T MRI to quantify the permanent grey and white matter damage from TBI will give insight into whether reduction in cognitive reserve or direct traumatic damage might explain the increased risk of dementia reported from case record based epidemiological studies. A no-cost study extension with widening of inclusion to include other military veterans will be requested in order to reach the veterans target of 50 with TBI and complete the 7T MRI after the Covid delay.

15. SUBJECT TERMS

Traumatic brain injury. Dementia. Amyloid. Tau. Positron emission tomography. Vietnam veterans. Motor vehicle accident. Alzheimer’s disease.

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Retrospective studies suggest that traumatic brain injury (TBI) increases the risk of Alzheimer’s disease (AD) four-fold. This has not been supported by recent PET imaging studies in Vietnam War veterans. PET scanning to measure the proteins Amyloid and Tau are the key predictors of future AD. It is these abnormal protein deposits that define AD. However, PET TBI studies have had small cohorts and have not used the latest generation of more sensitive imaging biomarkers. We will use the latest generation of PET imaging and 7 Tesla MRI to measure AD pathology. We will study 150 elderly TBI subjects and 100 age-matched controls. In addition, psychological testing will be carried out such that the imaging results can be tested for correlation with clinical endpoints.

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

Traumatic brain injury. Dementia. Amyloid. Tau. Positron emission tomography. Vietnam veterans. Motor vehicle accident. Alzheimer’s disease.

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.

The SOW had the following Tasks to be completed.

Major Task One: IRB amendments – **done and all approved.** Employ Research assistants – **done.**
Recruit 150 TBI and 100 controls over three years – **On schedule - 123 TBI and 82 controls recruited at end Yr 2.**

Major Task 2: 250 Tau and amyloid PET completed and transferred to FITBIR over 3 years – 123 TBI and 82 controls scanned to date. FITBIR transfer commenced. **Yr 2 targets achieved.**

Major Task 3: 250 7T MRI over 3 years – **delayed due to covid** but scans have commenced.

Major Task 4: Neuropsychological/psychological evaluations in 250 subjects over 3 years – 123 TBI and 82 controls evaluated to date. FITBIR transfer commenced. **Yr 2 target achieved.**

Major Task 5: Data Analysis, presentation and publication - Manuscript on amyloid and tau PET in MVA TBI **under review.** Cognitive data on MVA cohort published - *Amelia J Hicks, Gershon Spitz, Christopher C Rowe, et al. Does cognitive decline occur decades after a moderate to severe traumatic brain injury? A prospective controlled study. Neuropsychological Rehabilitation 2021; DOI: [10.1080/09602011.2021.1914674](https://doi.org/10.1080/09602011.2021.1914674)*

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.

Major Activities – recruitment, amyloid and tau PET scans, 3T MRI scans and psychological/cognitive testing of subjects with TBI due to motor vehicle accident or military service and matching controls. Commence FITBIR data upload and 7T MRI.

Specific Objectives – achieve 80% of recruitment and assessment (target is 150 TBI and 100 controls) by end of year 2. Commence data analysis and present findings at conferences. Prepare manuscripts. PhD student (Amelia Hicks) to complete sufficient assessments to meet requirements for her PhD thesis.

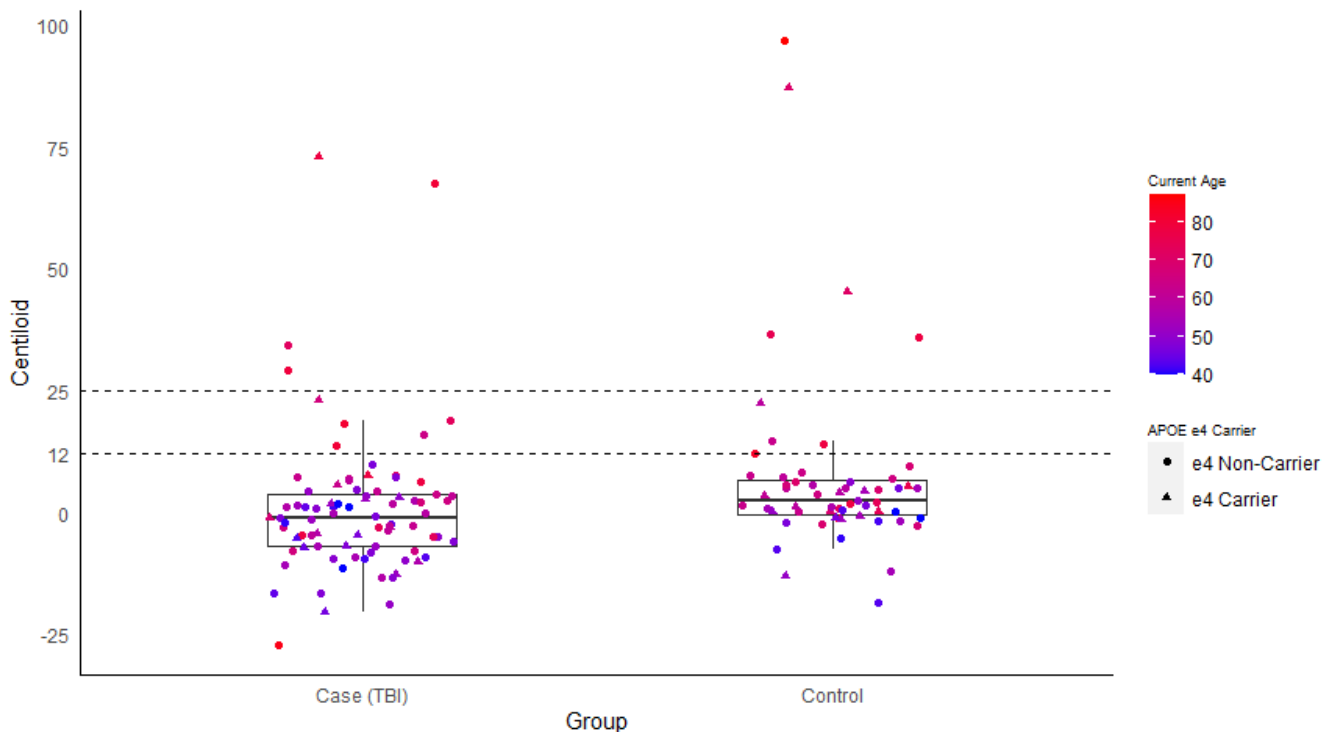
Key Outcomes – despite Covid disruption, recruitment and completed assessments reached 123 of 150 TBI target (82%) and 82 of 100 controls target (82%). PhD student had sufficient data to progress her PhD thesis and this was submitted in late 2021 and passed in March 2022. A manuscript reporting the findings in the MVA TBI and controls was submitted. It is undergoing assessment of the response to reviewer’s comments at present for the journal Neurology.

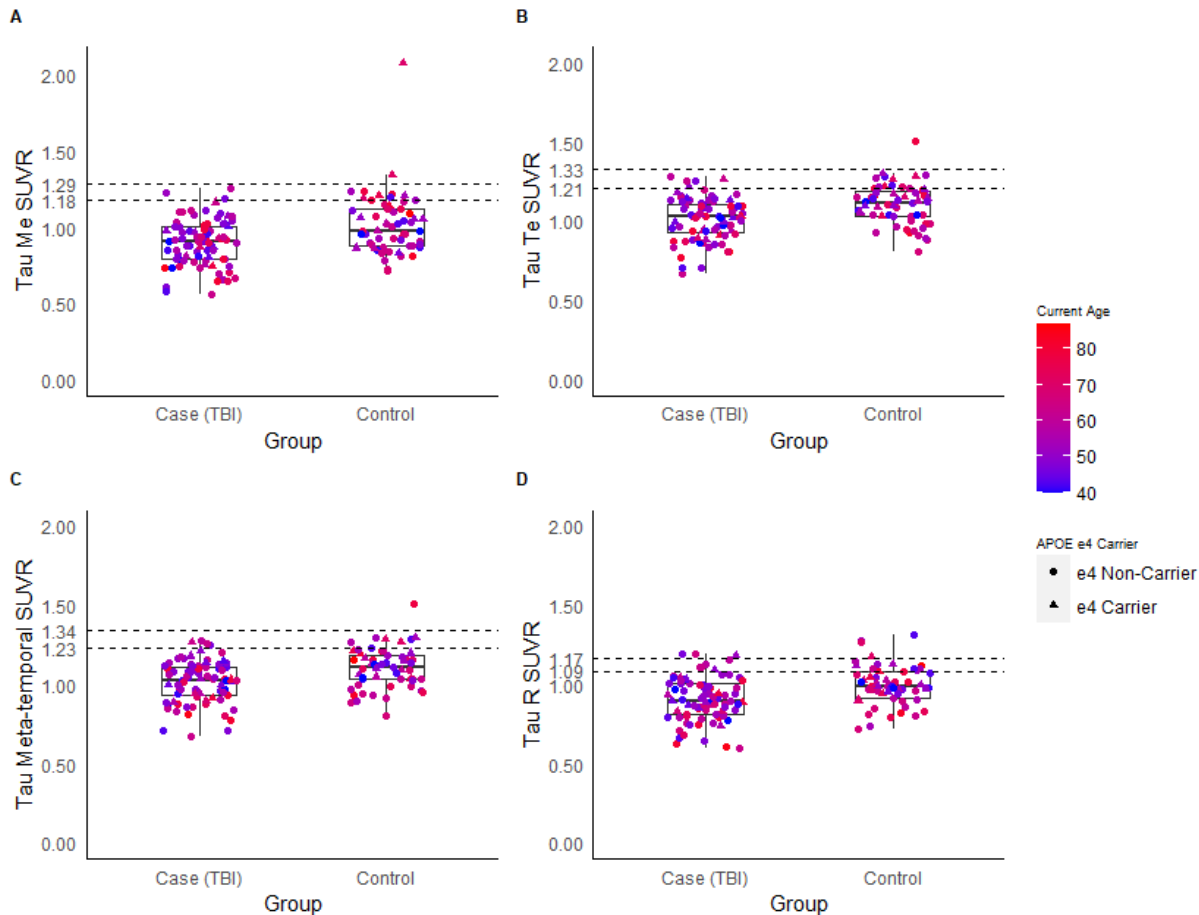
Publications:

Publication 1: Hicks AJ, Spitz G, Rowe CC, Roberts CM, McKenzie DP, Ponsford JL. Does cognitive decline occur decades after moderate to severe traumatic brain injury? A prospective controlled study. *Neuropsychol Rehabil.* 2021 Apr 15:1-20. doi: 10.1080/09602011.2021.1914674. Epub ahead of print. PMID: 33858304.

Publication 2: Under Review. Amelia J Hicks, Jennie L Ponsford, Gershon Spitz, Vincent Doré, Natasha Krishnadas, Caroline Roberts, Christopher C Rowe. Amyloid- β and tau imaging in chronic traumatic brain injury: A case-control study. *Neurology* 2022. Under review.

Selected figures from Publication 2 are shown below. Amyloid and tau PET results.





Amyloid and tau PET results are shown for the MVA TBI subjects recruited to date vs age matched healthy controls. There is no increase in tau or amyloid in the MVA TBI all of whom sustained moderate or severe non-penetrating TBI at least a decade before participation. From manuscript under review - *Amelia J Hicks, Jennie Ponsford, Gershon Spits, Spitz Vincent Doré, Natasha Krishnadas, Caroline Roberts, Christopher C Rowe. Amyloid- β and tau imaging in chronic traumatic brain injury: A case-control study.*

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.

PhD candidate Amelia Hicks based her PhD on this study and submitted her thesis for assessment in late 2021 and it was passed in March 2022.

PhD candidate Natasha Krishnadas MD has used some of the tau imaging data in her thesis on the role of tau imaging in Alzheimer's disease. Thesis is submitted and under review.

Final year medical student Robert Torode studied MRI findings in TBI for his research elective and drafted a paper on his findings.

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.

Data has been presented to the Combat Sports council of Victoria, Australia. The project and early results have been discussed on a Melbourne morning radio show.

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.

Complete the recruitment, analysis and publication of results. A new recruitment campaign has been launched through news media, Returned Services League clubs and Freemasons. However, to meet the target of 50 military veterans with service related TBI more than a decade ago, and complete the 7T MRI scans, a no cost extension will be required with an amendment to include non-Vietnam war veterans.

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).

Analysis of data to date should reassure the general public and combat veterans that traumatic brain injury does not cause Alzheimer’s disease. Alternative mechanisms for the reported increase in dementia in veterans and others with a history of TBI need to be explored. Possible explanations include loss of brain reserve/resilience so that dementia occurs in an earlier pathological stage of Alzheimer’s disease or that non-AD pathology such as TDP-43 is increased by TBI.

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.*

Data will be available to other entities through FITBIR.

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.*

Analysis of data to date should reassure the general public and combat veterans that traumatic brain injury does not cause Alzheimer’s disease.

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:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Problems have arisen due to Covid. 1. Delay in recruitment of veterans with TBI. 2. Delay in commencement of 7T MRI as the facility was shut during prolonged lock-downs. More controls for the MVA TBI cohort were recruited (65 instead of 30) as the planned AIBL controls were too old to age match to the MVA TBI cohort. This required more PET scanning (the AIBL controls are previously scanned) but the cost has been accommodated within the existing budget and it has produced a better control population.

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.

Covid pandemic closed the study for 9 months in 2020. The study returned to operation in early 2021 except at the 7T site but was closed again several months later as another Covid wave developed. Study recommenced in August for subjects who were fully vaccinated.

Consequently recruitment of veterans with TBI and 7T MRI scanning is behind schedule.

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.

Covid has delayed expenditure on 7T MRI. As amyloid and tau PET and neuropsychological evaluations remain globally on target with 82% of TBI and controls completed by end of year 2, these areas of expenditure remain ahead of the annual budget but are consistent with the total study expenditure. The brought forward PET expenditure almost balances the reduced 7T MRI expenditure at end of year two.

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

Nil.

Significant changes in use or care of vertebrate animals

Nil.

Significant changes in use of biohazards and/or select agents

Nil.

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).

Publication 1: Hicks AJ, Spitz G, Rowe CC, Roberts CM, McKenzie DP, Ponsford JL. Does cognitive decline occur decades after moderate to severe traumatic brain injury? A prospective controlled study. *Neuropsychol Rehabil.* 2021 Apr 15:1-20. doi: 10.1080/09602011.2021.1914674. Epub ahead of print. PMID: 33858304.

Publication 2: Under Review. Amelia J Hicks, Jennie L Ponsford, Gershon Spitz, Vincent Doré, Natasha Krishnadas, Caroline Roberts, Christopher C Rowe. Amyloid- β and tau imaging in chronic traumatic brain injury: A case-control study. **Neurology** 2022. Under review.

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).

PhD thesis titled: Chronic effects of traumatic brain injury on cognition and Alzheimer's Disease pathology. Author Amelia Hicks Monash University.

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.

Nil

- **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.

Nil

- **Technologies or techniques**

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

Nil

- **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.

Nil

- **Other Products**

1. Cognitive, clinical, PET and MRI scans and data.
2. Blood samples in liquid nitrogen storage awaiting further analysis and available for collaborative research.
3. The Melbourne Brain Injury Questionnaire was developed to document and quantify TBI for former military personnel, contact sports participants and the general public.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

*Name: Amelia Hicks
Project Role: PhD Student
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 20
Contribution to Project: Ms. Hicks has performed work in the area of recruitment, cognitive testing and analysis of the MVA TBI cohort.*

*Name: Vincent Dore PhD
Project Role: Senior Researcher
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: Dr. Dore has performed work in the area of PET data analysis.*

*Name: Natasha Krishnadas MD
Project Role: PhD Student
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 4
Contribution to Project: Dr. Krishnadas has performed work in the area of medical assessment of participants and analysis of the veterans and MVA TBI cohort data.*

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.

Nothing to report.

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: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable;*

however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.