

**AWARD NUMBER:** W81XWH-22-2-0043

**TITLE:** Blood-Based Biomarkers of Traumatic Brain Injury and Related Vascular Dementia

**PRINCIPAL INVESTIGATOR:** Dr. Sara Lippa

**CONTRACTING ORGANIZATION:** Henry Jackson Foundation for the Advancement of Military Medicine (HJF)

**REPORT DATE:** OCTOBER 2023

**TYPE OF REPORT:** Approved for Public Release; Distribution Unlimited

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

**DISTRIBUTION STATEMENT:** Approved for public release; distribution is unlimited.

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

*Form Approved*  
**OMB No. 0704-0188**

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<b>1. REPORT DATE</b> OCTOBER 2023		<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 1 SEPT 2022 - 31 AUG 2023	
<b>4. TITLE AND SUBTITLE</b> Blood-based Biomarkers of Traumatic Brain Injury and Related Vascular Dementia				<b>5a. CONTRACT NUMBER</b> W81XWH-22-2-0043	
				<b>5b. GRANT NUMBER</b>	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Dr. Sara Lippa  E-Mail: sara.m.lippa.civ@health.mil				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b>  Henry M. Jackson Foundation, for the Adv. of Mil. Med. 6720-A Rockledge Dr. STE 100 Bethesda, MD 20817				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> This study focuses on the association of traumatic brain injury (TBI) exposure with blood, neuroimaging, and cognitive biomarkers of TBI, traumatic cerebral vascular injury (TCVI), and cerebrovascular dysfunction. TCVI is a frequent consequence of TBI and may underlie a significant portion of chronic disability following TBI, including the risk of progression to vascular dementia. The study aims to characterize these unique biomarkers as well as their relationship to TBI history. It also aims to assess their ability to predict cognitive decline and changes in structural neuroimaging. Study agreements are still in progress and recruitment will soon begin.					
<b>15. SUBJECT TERMS</b> Traumatic brain injury; traumatic cerebrovascular injury; cognition; blood biomarkers; neuroimaging					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b>
<b>a. REPORT</b>	<b>b. ABSTRACT</b>	<b>c. THIS PAGE</b>			<b>19b. TELEPHONE NUMBER</b> (include area code)
U	U	U	UU	9	

## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4-6
4. Impact	6
5. Changes/Problems	6-7
6. Products	7-8
7. Participants & Other Collaborating Organizations	8-9
8. Special Reporting Requirements	9
9. Appendices	9

## 1. INTRODUCTION:

This study focuses on the association of traumatic brain injury (TBI) exposure with blood, neuroimaging, and cognitive biomarkers of TBI, traumatic cerebral vascular injury (TCVI), and cerebrovascular dysfunction. TCVI is a frequent consequence of TBI and may underlie a significant portion of chronic disability following TBI, including the risk of progression to vascular dementia. The study aims to characterize these unique biomarkers as well as their relationship to TBI history. It also aims to assess their ability to predict cognitive decline and changes in structural neuroimaging.

## 2. KEYWORDS:

Traumatic brain injury; traumatic cerebrovascular injury; cognition; blood biomarkers; neuroimaging

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

This research project will characterize unique blood biomarkers in 300 SMs/Veterans who previously participated in the National Intrepid Center of Excellence (NICoE) Intensive Outpatient Program (IOP) or 15-Year Natural History study (NatHx). It will also examine the relationship between vascular blood biomarkers of TBI and cognitive performance and how this relationship is modified by inflammatory and neurodegenerative biomarkers as well as identify a panel of blood biomarkers that correlates with cognitive functioning.

The study will do this by leveraging previously collected (NICoE/NatHx/DoD biorepository) serum samples to investigate how TBI characteristics impact vascular blood biomarkers over time. It will also examine how changes in remote blood biomarkers relate to novel neuroimaging, changes in structural neuroimaging, and changes in cognitive performance over time. Additionally, the study will develop a panel of blood biomarkers that can predict cognitive decline, volume loss, and white matter changes. Finally, the study will examine how neuroimaging biomarkers alone and in combination with vascular blood biomarkers relate to CDR and cognitive performance. This will be done by identifying a multimodal panel of blood and imaging biomarkers that correlates with cognitive functioning.

In order to accomplish the above goals, the project has four major tasks:

Major Task 1: Protocol Preparation and Approvals

Major Task 2: Coordinate Study Staff

Major Task 3: Enroll and assess participants

Major Task 4: Biomarker Assays and Data Analysis

### What was accomplished under these goals?

Major Task 1: Protocol Preparation and Approvals

1. Prepared WRNMMC protocol package for scientific review (a requirement for full IRB submission) and received WRNMMC scientific approval letter 27JAN2023. First-level approval obtained by JHU IRB JUN 2023.
2. Second-level OHRO approval obtained for WRNMMC and JHU JUL2023.
3. Submitted protocol modification including personnel changes and protocol changes requested by HJF and DoD Serum Repository (August 2023).
4. Drafted, refined and finalized study CRFs and ensured PDF fillable and exportable capabilities (Sept 2022-Mar 2023)

Major Task 1: Protocol Preparation and Approvals (continued)

5. Discussed participant reimbursement and travel procedures with contracting company (25-Oct-2022) and drafted associated SOPs (Nov 2022).
6. Acquisition of neuropsychological assessment and phlebotomy supplies, as well as storage for supplies (FEB2023). Included in neuropsychological assessment supplies is the installment of neuropsychological assessment software installed on study laptops (APR2023).
7. Began process of requesting account through FITBIR for eventual data upload (Feb 2023)
8. Administrative approval through ClinicalTrials.gov obtained SEP2023. Awaiting registration.
9. Initiated contact with DoD serum repository (Feb 2023)
10. Began building electronic Regulatory Binder (Mar 2023)
11. Completed study Manual of Procedures (MOP) and continued creation and refinement of study SOPs, including conversations with contracting company regarding participant travel and reimbursement.
12. Ongoing creation and refinement of study database shell.
13. Movement through waiting list for CRADA/MTA draft creation (August 2023)
14. Ongoing weekly conference calls to discuss various logistics to approval and study set-up.

Major Task 2: Coordinate Study Staff

1. Advertised and interviewed for Research Coordinator (SEP2022)
2. Coordinated for space allocation for new staff (SEP2022)
3. Hired Research Coordinator (12OCT2022) and research assistant (30JAN2023)
4. Staff training completed and ongoing.

Major Task 3: Enroll and assess participants

- No associated accomplishments this reporting period.

Major Task 4: Biomarker Assays and Data Analysis

- No associated accomplishments this reporting period.

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

- Ongoing training completed by PI and study coordinator in order to become more familiar with IRB and Department of Research Program (DRP) processes. Trainings provided by the DRP at Walter Reed National Military Medical Center.
- Ongoing mentorship between PI and study AI (Dr. Kimbra Kenney).
- Training courses completed by PI and study coordinator in order to become proficient in conducting the CAPS-5 interview with study participants. Trainings provided by the Department of Veterans Affairs.
- Training and mentorship between PI and research coordinator regarding skills related to use of Microsoft Excel and statistical package software. This information will be used in database creation and to assist in future data analyses.
- PI attended the Annual meeting of the American Academy of Clinical Neuropsychology, as well as several workshops and seminars offered through Walter Reed, INTBIR, and DHA.
- Research coordinator attended workshops and seminars focused on TBI and data management offered through Walter Reed and DHA.

**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?**

After completion of the CRADA and receipt of a start letter:

- Begin recruitment and data collection.
- Continue coordination with partnering studies (Natural History Study and NICOE Core Neuroimaging Protocol) in regards to travel/lodging logistics and sharing of participant data.
- Solidify all steps of a participant visit and complete a mock run-through of a complete visit.
- Establish contact with FITBIR in order to solidify a study database shell and FITBIR upload procedures.

**4. IMPACT: What was the impact on the development of the principal discipline(s) of the project?**

Nothing to Report.

**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:**

Throughout the study approval process, there has been a shortage of staff at the WRNMMC Department of Research Programs. This has caused significant delays in the drafting of legal agreements which are required in order to receive a study start letter. As such, the start date of the project has been delayed.

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

The project's CRADA is currently moving through the waiting list and a draft will optimistically be completed by late September 2023.

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

The overhead cost requested by Walter Reed National Military Medical Center has decreased from 27% to 24%.

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

**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**

**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?

Name: Dr. Sara Lippa

Project Role: PI

Researcher Identifier: ORCID ID 0000-0002-6352-7577

Nearest person month worked: 3

Contribution to Project: Dr. Lippa is the principal investigator of the study and the recipient of the grant award. She has completed all regulatory forms thus far, developed the protocol, consent form, and all other project-related documents, and coordinated with other entities and sites who will be involved with the project. She has also hired personnel who will be working on the project.

Name: Dr. Kimbra Kenney

Project Role: Associate Investigator

Researcher Identifier: ORCID ID 0000-0002-8138-7539

Nearest person month worked: 1

Contribution to Project:

Dr. Kenney has assisted with all portions of study development thus far and has contributed her wealth of knowledge regarding study development and IRB protocol initiation, submission and review.

Name: Megan Glazer  
Project Role: Clinical Research Coordinator  
Researcher Identifier: N/A

Nearest Person month worked: 10

Contribution to Project: Ms. Glazer has assisted in completing forms required for regulatory purposes, has addressed IRB protocol and consent stipulations, created drafts of project-related documents, has assisted in acquisition of supplies and materials required for study initiation, and has trained on neuropsychological assessments and psychological interviews to be used in the study.

Name: Chiara Racioppi  
Project Role: Research Assistant  
Researcher Identifier: N/A

Nearest Person month worked: 4

Contribution to Project: Ms. Racioppi has worked to ensure a smooth transition with the partnering Natural History and NICoE Core Neuroimaging Studies. She has been training on recruitment, consent, travel/lodging coordination, data entry, and other study procedures to ensure we can recruit and collect data on participants as soon as agreements are in place and a start letter is received.

**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?**

Nothing to report.

## **8. SPECIAL REPORTING REQUIREMENTS**

**COLLABORATIVE AWARDS:** N/A

**QUAD CHARTS:** See attached.

## **9. APPENDICES:** N/A