AWARD NUMBER: W81XWH-22-1-1106

TITLE: Multi-Institutional Phase 2/3 Trial of Fresh Frozen Plasma (FFP) in Patients with Moderate to Severe Traumatic Brain Injury (TBI)

PRINCIPAL INVESTIGATOR: Hasan Alam, MD

CONTRACTING ORGANIZATION: Northwestern University

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TYPE OF REPORT: Annual

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

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
OCTOBER 2023	Annual	30SEPT2022 - 29SEPT2023

4. TITLE AND SUBTITLE

Multi-Institutional Phase 2/3 Trial of Fresh Frozen Plasma (FFP) in Patients with Moderate to Severe Traumatic Brain Injury (TBI)

5a. CONTRACT NUMBER
W81XWH-22-1-1106

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Hasan Alam, MD
Sharnia Lashley, MS

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northwestern University
633 Clark Street
Evanston, IL 60208-001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development 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 is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study will be a Phase 2/3, randomized, multicenter study performed under Exception From Informed Consent (EFIC) to evaluate the efficacy of administration of FFP in subjects with moderate to severe TBI across eight sites with a history of performing studies under EFIC. The study aims to determine whether administration of 2 units of FFP in patients with moderate to severe TBI due to cerebral contusions attenuates hemorrhagic and/or ischemic progression of brain lesions during the early (24 hours) post-injury period.

15. SUBJECT TERMS

Trauma, TBI, traumatic brain injury, moderate, severe, hemorrhagic progression, ischemic progression, brain lesion, post-injury, cerebral contusion

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	16	19b. TELEPHONE NUMBER *(Include area code)*

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1. INTRODUCTION:

This clinical trial aims to determine whether investigational administration of 2 units of fresh frozen plasma (FFP) in patients with moderate to severe traumatic brain injury (TB) due to cerebral contusions, attenuates hemorrhagic and/or ischemic progression of brain lesions during the first 24 hours post-injury period. The safety of the administration will be documented using treatment emergent adverse events in those with no FFP requirement for resuscitation. Treatment impact will be measured using the Disability Rating Score (DRS) and Glascow Coma Scale (GCS) at 24 hours and 6 months, along with the Extended Glasgow Outcome Score (GOS-E) at 6 months. Patient intensive-care-free days, mortality and hospital neurologic and functional discharge status will be measured as well.

2. KEYWORDS:

Trauma, TBI, traumatic brain injury, moderate, severe, hemorrhagic progression, ischemic progression, brain lesion, post-injury, cerebral contusion

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Year one goals included the following:
Major Task : Complete the organizational, contractual, and regulatory work to start the clinical trial
Sub aim 1 Tasks: Complete all university/hospital-level regulatory and contractual requirements for clinical trial
Milestones Achieved:
Recruit Project Manager and Research Staff – **Completed**
Hold the initial Project Launch Meeting - **Completed**
Coordination with NUCATS –**Completed**
Local site CTAs and NDAs – **Initiated discussions**
Contracts with BSA and c-IRB signed – **Completed**
Data collection instruments finalized before external submissions – **50% Completed** (pending final protocol approval)
COT and clinical site monitoring plan finalized – **95% Completed**
DSMB setup completed – **75% Completed**
Finalized selection of any further CS **– N/A**
Local IRB at all CS consulted –**75% Completed**
All DSMB members recruited – **75% Competed** with chair established and 75% of members confirmed
Finalized Organization Chart, Management Plan, Data Management and Evaluation Plan: **- 90% Completed with finalization of plans pending regulatory approvals**
Site establishment plans finalized: – **95% Completed** awaiting regulatory approvals to confirm needed procedures
Sub aim 2 Tasks: Complete all government-level regulatory and contractual requirements for clinical trial
Milestones Achieved:
Study protocol approved for submission to FDA by DoD – N/A (DoD indicated submission proceeds FDA and IRB approval)
Pre-IND communication with FDA completed – **Completed**
ClinicalTrials.gov registration confirmed – **Completed**

What was accomplished under these goals?

Sub aim 1 Tasks: Complete all university/hospital-level regulatory and contractual requirements for clinical trial
Sub aim 2 Tasks: Complete all government-level regulatory and contractual requirements for clinical trial
Most major statement of work (SOW) milestone under Sub aim 1 and 2 tasks, were achieved as listed above including recruitment, project launch, contract finalization and local department and team coordination. Near completion activities include site establishment, data management, and evaluation plans. Awaiting final word from one potential DSMB team member, the DSMB is almost established, and the charter draft is in progress as a result. Response regarding local clinical site required IRB procedures are pending for two sites. Clinical trial agreement timelines fall later in the process than indicated on the SOW. We learned that the DOD only required a submission (HRPO) after FDA IND and IRB trial approval.

At the SOW creation, it was thought that site visits would occur earlier in the planning process because it was thought IRB submission and approval could precede FDA approval. That proved not to be the case, as determined by an IRB submission attempt in the Spring of the year. We achieved a pre-IND meeting request and were able to avoid the actual pre-IND meeting given the FDA requested clarifications and changes were accomplished The FDA meeting request interactions resulted in exclusion criteria and protocol revisions that included the inclusion of pregnant participants. The FDA IND preparation followed, though slightly behind our anticipated timeline as we gathered accurate Statement of Investigator and other investigator documents for eight trial sites. The ClinicalTrials.gov registration application was completed, and the trial was published to ClinicalTrials.gov during the final quarter of the year.

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?

During the next reporting period, we expect to submit the IND application to the FDA, receive IND approval, re-submit the initial study application to the single IRB (sIRB), receive IRB approval, distribute IRB approved documents to the sites, and start community consultations within the next two quarters and start the clinical trial phase activities by the third quarter of 2024.

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:

Nothing to Report.

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

Nothing to Report.

Changes that had a significant impact on expenditures

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 of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

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

Nothing to Report.

Journal publications.

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

Nothing to Report.

Other publications, conference papers and presentations.

Manuscript Submission: August 30, 2023
Authors: Marjorie R Liggett, Sharnia Lashley, Hasan B Alam
Title: Plasma Therapy for Traumatic Brain Injury: Rationale for a Prospective Randomized Trial
Journal: TRANSFUSION

- **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:	*Sharnia Lashley*
Project Role:	*Project Manager*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*12*
Contribution to Project:	*Over the course of the year Ms. Lashley performed work that supported DOD, FDA and IRB submission activities, including content generation, collection, review, correction and revision and in the instance of the initial IRB submission, provided the content, filled out the application and made the initial and post-pre-review IRB submission. Ms. Lashley met with contact and collaborated with trial site leads to select the trial short name and logo during year 1 of the planning phase. She filled the continuous role of liaison between collaborating sites and the regulatory consultant, Broom Street associates to gather regulatory documents and content in advance of trial startup. Ms. Lashley drafted technical report content, generated, and disseminated a monthly news update/newsletter and attended and provided content for weekly, bi-weekly and monthly meetings.*

Name:	*Hasan Alam*
Project Role:	*Trial Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*No change*

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?

Collaborating Institutions
Vanderbilt University – Nashville, TN
University of Southern California - Los Angeles, CA
Oregon Health and Science University – Portland, OR
Medical College of Wisconsin – Milwaukee, WI
University of Texas Southwestern – Dallas, TX
University of California, Davis – Sacramento, CA
University of Alabama at Birmingham – Birmingham, AL

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to Report

9. APPENDIX 1

OMB Number: 0925-0770
Expiration Date: 09/30/2024

PHS Inclusion Enrollment Report

1. * Inclusion Enrollment Report Title

Multi-institutional Phase 2/3 Trial of Fresh Frozen Plasma (FFP) in Patients with Moderate to Severe Traumatic Brain Injury (TBI)

2. * Using an Existing Dataset or Resource

Yes ☐ No ☒

3. * Enrollment Location Type

Domestic ☒ Foreign ☐

4. Enrollment Country(ies)

x USA: UNITED STATES

Add New Country

5. Enrollment Location(s)

Northwestern University; Vanderbilt University; University of Southern California; Oregon Health and Science University; Medical College of Wisconsin; University of Texas Southwestern; University of California, Davis;

6. Comments

Planned

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	7	8	0	1	16
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	15	36	0	1	52
White	51	87	17	32	187
More than One Race	1	4	1	2	8
Total	74	136	18	36	264