AWARD NUMBER: W81XWH-15-2-0039

TITLE: A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood

PRINCIPAL INVESTIGATOR: Donald Jenkins, M.D.

CONTRACTING ORGANIZATION: NATIONAL TRAUMA INSTITUTE
San Antonio, TX 78230

REPORT DATE: September 2018

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
September 2018	Annual	25Aug2017 - 24Aug2018

4. TITLE AND SUBTITLE

A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-2-0039

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Donald Jenkins

Email: jenkinsd4@uthscsa.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

National Trauma Institute
9901 IH 10 West, Suite 720
San Antonio, Tx 78230

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel 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 Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT Resuscitation protocols for trauma patients presenting with significant bleeding utilize administration of components of blood including RBCs, plasma, and platelets. Despite improvements in emergency surgery and critical care, trauma patients with severe bleeding still suffer from high incidence of complications and death compared to patients that require fewer or no transfusions. Recent studies from military centers indicate that transfusion of FWB may be more beneficial than individual blood components in patients with severe hemorrhage. This has not been studied in civilian trauma patients mainly due to the technical difficulties and costs. We propose a feasibility and hospital outcomes study using FWB (storage time of 5 days) for resuscitating trauma patients with significant bleeding. A cohort of adult trauma patients presenting with severe hemorrhage and receiving resuscitation with FWB will be prospectively compared to a control group of patients receiving standard component therapy. The shelf-life of whole blood, cost of treatment, levels of clotting and inflammatory markers in patient's blood samples, as well as the incidence of persistent bleeding, development of blood clots, infections, and mortality will be compared between the two groups. This study is designed to determine whether FWB transfusions are feasible in a civilian trauma center and to determine whether resuscitation using FWB is superior to component therapy in patients with severe hemorrhage.

15. SUBJECT TERMS

None listed

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	12	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

NATIONAL TRAUMA INSTITUTE ANNUAL REPORT

Sub-award No:	NTI-JWMRP_201501	Report Date:	9/25/18
Reporting Period:	9/1/2017 – 8/31/2018	PI Name:	Henry Cryer, M.D.
Type of Report:	☒ Annual ☐ Final		
Institution:	UCLA, Department of Surgery		
Project Title:	Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes		
Prepared for:	National Trauma Institute, 9901 IH 10, Suite 720, San Antonio, Texas 78230		
Distribution Statement:	☒ distribution unlimited ☐ distribution limited, contains proprietary information		
	The views, opinions and/or findings contained in this report are those of the author (s) and should not be construed as an official National Trauma Institute position or statement.		

UCLA

UCLA Enrollment

Target N=60

	Recruited	**Screened**	**Enrolled**	**Completed**
Cumulative	30	30	30	30

*Please note that the 4th quarter enrollment numbers were not provided at the time of this report. We will submit updated enrollment numbers when received from UCLA.

1. INTRODUCTION:

Most current massive transfusion protocols attempt to treat the early coagulopathic state induced by severe injury and hemorrhagic shock with transfusion of RBC, plasma, and platelets in a 1:1:1 ratio replicating whole blood. At least 2 institutions have now begun to initiate resuscitation of adult male patients with stored whole blood as a standard of care and we intend to do the same while studying the efficacy and feasibility of the change in practice. The main hypothesis behind this study is that transfusion of whole blood (WB) rather than attempted reconstitution from its banked components is safer, more efficient and effective treatment of hemorrhagic shock following injury and will result in less frequent development of clinical coagulopathy and subsequent mortality. The purpose of this study is to investigate the feasibility of developing a system to collect, store, and deliver whole blood for trauma resuscitations in our civilian trauma center. The universal donor blood type for patients with unknown blood type is type O positive blood for males and O negative for females. Because O negative blood is rare we plan to initiate our change in practice in adult male patients and later extend it to female patients if feasible. We will determine the effects of WB transfusion in adult male patients compared to transfusion of RBC, plasma, and platelets in a 1:1:1 ratio in non adult male patients on markers of coagulation, fibrinolysis, and inflammation, as well as the development of complications and hospital mortality following severe injury. One recent pilot study comparing modified whole blood to component therapy in severely injured patients (Cotton et al. Ann Surg.258: 527-533, 2013) did not show a difference in blood product usage or mortality between groups. However, they did not look at the effects of the 2 resuscitation schemes on coagulation function as we propose to do. In addition, in that study both groups received room temperature apheresis platelets because their leukoreduction process removed platelets. Our study proposes to use a leukoreduction process that spares platelets so that patients will receive only whole blood. Another study (Yazer et al JTrauma 81(1):21-6. doi: 10.1097 2016) described a change in practice process improvement initiative demonstrating the safety of transfusing up to 2 units of low titer, platelet sparing leukocyte-reduced whole blood stored for up to 10 days for 145 male patients. We will begin our change in practice with storage of whole blood up to 10 days. Specific aims are to: 1. Determine the appropriate shelf life of FWB that has been leukoreduced with a platelet sparing filter by measuring changes in levels of coagulation factors and global clotting potential of banked units over time; 2. Prospectively determine the effectiveness of trauma resuscitation using FWB compared to component therapy and its effects on transfusion requirements and variables known to reflect potential and actual clotting capacity including markers of coagulation, fibrinolysis, inflammation, platelet function and global hemostatic potential post transfusion, as well as hospital outcomes including development of coagulopathy, infection, venous thromboembolism (VTE), multiple organ failure (MOF), and mortality; and 3. Test the feasibility and implementation of a system to provide FWB for resuscitation of trauma patients in hemorrhagic shock in civilian trauma centers by monitoring cost, storage needs, frequency of blood collection, number of donors, inventory, utilization and wastage of unused units.

2. KEYWORDS: (limit to 20 words).
Treatment; Hemorrhagic Shock; Transfusion; blood components; products; RBC; Plasma; Platelets; Fresh Whole Blood; Injury; leukoreduction; resuscitation; markers of coagulation; fibrinolysis

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

What were the major goals of the project?
Include dates or percent of completion.

Aims and Major Goals	Timeline in Months	Completion Date	% Complete
Specific Aim 1: Determine the shelf life of whole blood months			
Collection of whole blood units	1-9		5%
Testing of whole blood units for coagulation markers	1-9		0%
Analysis of in vitro study data	6-12		0%
Specific Aim 2: Determine the effectiveness of whole blood compared to component therapy			
Enrollment of trauma patients into the control arm, consisting of component therapy resuscitation	13-30		60%
Collection of whole blood units from volunteer blood donors	19-30		60%
Enrollment of trauma patients into the intervention group	19-30		60%
Blood sample collection from trauma patients	13-30		60%
Testing of blood samples from trauma patients	13-30		60%
Review of unexpected or adverse events by the medical monitor	13-30	Ongoing	60%
Data analysis	13-33		25%
Specific Aim 3: Determine the feasibility of providing whole blood for resuscitation of hemorrhagic shock			
Collection of data regarding whole blood utilization and cost	13-27		60%
Complete blood bank data base	28-30		60%
Analyze blood bank data base	28-33		50%
Other Major Tasks:			
Identification of communities in the UCLA catchment area	1-3		N/A
Advertisements for community meetings and focus groups	1-6		N/A
Hold community meetings and focus groups	3-6		N/A
IRB approval for Exemption from Informed Consent	4-9		N/A
Secretary General of the Army approval for Exemption from Informed Consent	7-18		N/A
Finalize consent form & human subjects protocol	10-12	12/05/16	100%
Submit amendments, adverse events, and protocol deviations	As needed	Ongoing	100%
IRB continuing review	Annually	06/27/2017	100%
Research group meeting	Quarterly	Ongoing	100%

What was accomplished under these goals?

During the past year, we began and continue to enroll patients into both the control and whole blood arms of the study. Whole blood collection from the pool of identified low titer donors. A research assistant was brought in to complete in vitro studies for Aim 1. The study group continue to determine the feasibility of providing whole blood for resuscitation of hemorrhagic shock.

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

The project provided training to research resident Anaar Siletz in clinical trial design and management. It will also provided training to student research assistants identified through UCLA's Emergency Medicine Research Associate program who assist in identifying patients and collecting data.

How were the results disseminated to communities of interest?

Not applicable

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

The next year we will complete the enrollment of patients and testing of whole blood units. The determination of the shelf life of whole blood (Aim 1) will be completed in its entirety in the next year. Feasibility and cost-effectiveness data will be completed concurrently with enrollment of patients.

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?

The project has already led to a change in practice allowing whole blood for transfusion of male trauma patients at UCLA.

What was the impact on other disciplines?

The change in practice affects surgical, emergency department, and critical care disciplines.

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: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.:

Changes in approach and reasons for change

No changes reported.

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

The study was approved for a one year No Cost Extension. The study will be completed over the next year.

Changes that had a significant impact on expenditures

- None since prior annual report

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

- None

Specify the applicable Institutional Review Board approval dates.

- Continuing review submitted on July 13, 2018

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

  Journal publications. *List peer-reviewed article or paper citation; include 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.

  - Nothing to report

  Other publications, conference papers, and presentations. *Use an asterisk (*) if presentation produced a manuscript.*

  - Nothing to report

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

  - Not applicable

- Technologies or techniques

  - Not applicable

- Inventions, patent applications, and/or licenses

  - Not applicable

- Other Products

  - Not applicable

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	**Project Role**	**Nearest person month worked**	**% Effort**	**Contribution to the project**
Donald Jenkins	Principal Investigator	0.45	5% (Sept-May)	Oversight of entire project
Michelle Price	Research Director	0.075 0.30	2.5% (Sept-June) 10% (July-August)	Regulatory and research oversight and reporting
Lizette Villarreal	Program Manager	0.06 0.90	2% (Oct-Nov) 10% (Dec-August)	Regulatory oversight and coordination of reviews and reporting from site to NTI and from NTI to MRMC
Amy Flores	Controller	0.15 0.90	5% (Sept-Nov) 10% (Dec-August)	Grant expense tracking, invoice processing and payments.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
No

What other organizations were involved as partners?

Organization Type *(Academic institutions, other nonprofits, industrial or commercial firms, state or local governments)*	Organization Name	Location	Partner's contribution • *Financial support* • *In-kind support* • *Facilities*
Academic Institution	UCLA	757 Westwood Blvd , Los Angeles CA 90024	Facilities and bioinformatics support

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: Update and attach Quad Chart.

9. APPENDICES: none

Transfusion of Stored Fresh Whole Blood in a Civilian Trauma Center: A Prospective Evaluation of Feasibility and Outcomes

ERMS/Log Number: JW140027
Award Number: W81XWH-15-2-0039

Grant PI: Donald Jenkins **Study PI:** Henry M Cryer **Org:** UCLA **Award Amount:** $499,995

Study/Product Aim(s)

- Determine the shelf life of FWB
- Prospectively determine the effectiveness of trauma resuscitation using FWB compared to component therapy
- Test the feasibility and implementation of a system to provide FWB for resuscitation of trauma patients in hemorrhagic shock

Approach

After determining the shelf life of FWB, by measuring coagulation markers, trauma patients in hemorrhagic shock presenting to the ED will either receive component therapy or whole blood resuscitation. Blood samples, collected from time of presentation until 7 days after admission, will be analyzed and compared for markers of inflammation and coagulation. Clinical data, including blood transfusion requirements, development of coagulopathy, venous thromboembolism, infections, and mortality, will be collected and compared prospectively.

Non-filtered FWB stored at 4C retains functional global clotting capacity for up to 35 days, suggesting that FWB leukoreduced with a platelet-sparing filter, stored for prolonged periods of time, will be an acceptable stand-alone product for resuscitation from hemorrahagic shock.

Timeline and Cost

Activities CY	15	16	17	18
Determine the shelf life of FWB				$250
Determine the effectiveness of trauma resuscitation using FWB compared to component therapy				$150
Test the feasibility and implementation of a system to provide FWB for resuscitation of trauma patients in hemorrhagic shock				$100
Estimated Budget ($K)		**$250**	**$150**	**$100**

Updated: (09/25/18)

Goals

CY15 & 16 Goals – Determine the shelf life of FWB
☐Measure coagulation markers in stored FWB
☐Analyze data from in vitro study
☐Begin community consent process to get IRB and DoD approval for clinical study (No longer necessary)
☑Get IRB approval for the clinical study
CY17 Goals – Begin clinical study
☑Establish rolling inventory of banked whole blood
☑Enroll patients in control and experimental arms of the study
☐Measure coagulation markers in patient samples
CY18 Goals – Complete clinical study; Test feasibility of a system to provide for resuscitation of trauma patients in hemorrhagic shock
☐Analyze clinical sample data
☐Analyze data regarding whole blood utilization and cost