

AWARD NUMBER: **W81XWH-12-2-0028**

TITLE: **A Prospective, Randomized Investigation of "Plasma First Resuscitation" for Traumatic Hemorrhage and Attenuation of the Acute Coagulopathy of Trauma - PUPTH-IIA**

PRINCIPAL INVESTIGATOR: **Ernest E. Moore**

RECIPIENT: **University of Colorado Denver  
Aurora, CO 80045**

REPORT DATE: **March 19, 2019**

TYPE OF REPORT: **Annual Report**

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

DISTRIBUTION STATEMENT A: **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> MARCH 2019			<b>2. REPORT TYPE</b> Annual		<b>3. DATES COVERED</b> 20FEB2018 - 19FEB2019	
<b>4. TITLE AND SUBTITLE</b>  A Prospective, Randomized Investigation of "Plasma First Resuscitation" for Traumatic Hemorrhage and Attenuation of the Acute Coagulopathy of Trauma - PUPTH-IIA					<b>5a. CONTRACT NUMBER</b> W81XWH-12-2-0028	
					<b>5b. GRANT NUMBER</b>	
					<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b> Ernest E. Moore, MD, Jacob Feiler, Arsen Ghasabyan MD, MPH  E-Mail: <a href="mailto:ernest.moore@dhha.org">ernest.moore@dhha.org</a> , <a href="mailto:jacob.feiler@dhha.org">jacob.feiler@dhha.org</a> , <a href="mailto:arsen.ghasabyan@dhha.org">arsen.ghasabyan@dhha.org</a>					<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>  UNIVERSITY OF COLORADO DENVER 13001 E 17TH PLACE BLDG 500 W1126 AURORA CO 80045-2570					<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b>  U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012					<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Approved for Public Release; Distribution Unlimited					<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b>  The COMBAT (Control of Major Bleeding After Trauma) study is a randomized clinical trial evaluating the early administration of plasma, compared to the standard crystalloid. Over the past year, we have worked on refining our procedures and workflows, collecting accurate and timely data, ensuring regulatory compliance, and communicating with all study team personnel at Denver Health and the University of Colorado Anschutz Medical Campus. We have enrolled a total of 98 patients to-date and 41 patients this reporting year. We have collected over 4,500 samples this year, in addition to submitting our annual continuing review, publishing and presenting several papers.						
<b>15. SUBJECT TERMS</b> Trauma; coagulopathy; trauma-induced coagulopathy; plasma; resuscitation						
<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>	Unclassified	14	USAMRMC	
Unclassified	Unclassified	Unclassified			<b>19b. TELEPHONE NUMBER</b> (include area code)	

## **ABSTRACT**

The COMBAT study is a randomized clinical trial evaluating the early administration of plasma compared to the standard of care. Over the past year, we have worked on analyzing specimens and data, ensuring regulatory compliance, and communicating with all study team personnel at Denver Health and the University of Colorado Anschutz Medical Campus. No patient enrollment after March 2017. We submitted and received approval for our annual continuing review and published and presented several papers.

## Table of Contents

	<u>Page</u>
1. Introduction	3
2. Keywords	3
3. Overall Project Summary	3
4. Key Research Accomplishments	7
5. Conclusion	10
6. Publications, Abstracts, and Presentations	10
7. Inventions, Patents and Licenses	10
8. Reportable Outcomes	10
9. Other Achievements	10
10. References	11
11. Appendices	11

## 1. INTRODUCTION:

*This report includes April 1<sup>st</sup>, 2018 – March 31<sup>st</sup>, 2019.*

Bleeding is the most preventable cause of death in trauma patients. Coagulopathy has been documented in up to one third of trauma patients upon arrival to the emergency department. The mechanism of trauma induced coagulopathy (TIC) has yet to be elucidated. Presumptive early administration of plasma has been suggested to improve outcomes in observational studies, but no randomized clinical trial has been conducted to date comparing the administration of early plasma to the current standard of care. In this research study, trauma patients who meet eligibility criteria, defined as field systolic blood pressure (SBP)  $\leq 70$ mmHg or 71-90mmHg with HR  $\geq 108$ bpm, will be randomized to receive plasma or intravenous crystalloid, the current standard of care, as the initial resuscitation fluid. Our hypothesis is that the administration of plasma early will attenuate TIC, leading to improved outcomes.

## 2. KEYWORDS:

Trauma; coagulopathy; trauma-induced coagulopathy; plasma; resuscitation

## 3. OVERALL PROJECT SUMMARY:

### A. Sample Processing and Study Procedures

This past year, our study team has continued analyzing study specimens and data.

### B. Patient Enrollment and Sample Procurement

**Reporting Quarter:** No enrollment.

**Reporting Year:** No enrollment.

Table 1: Summary by Quarter, Year, and Total

<b>Term</b>	<b># of Patients Enrolled</b>	<b># of Samples Collected</b>
1/1/19 – 3/31/19	0	0
10/1/18 – 12/31/18	0	0
8/1/18 – 9/30/18	0	0
4/1/18 – 6/30/2018	0	0
Total for Reporting Year	0	0
Total Since Study Start	144	16821

During this reporting year, we analyzed an additional 120 patient samples by liquid chromatography tandem mass spectrometry. Some of these samples have been run in duplicated to determine analytical coefficients of variance.

**C. Unanticipated Problems and Patient Withdrawals**

**Reporting Quarter:** We did not have any unanticipated problems this quarter.

**Reporting Year:** We did not have any unanticipated problems this reporting year.

**D. Paramedic Training and Continuing Education**

**Reporting Quarter:** No paramedic training was held this reporting quarter.

**Reporting Year:** No paramedic training was held this reporting quarter.

**E. Study Devices and Equipment**

We completed the electrical upgrades in the lab: now we have five extra 208V dedicated circuits installed. Two -30C Helmer brand freezers are currently connected to these 208V outlets in the research lab as backup for our ultralow (-80C) freezers. With DoD approval we initiated a purchase of one -80C Helmer brand freezer to replace two failed freezers.

**F. Problems/Issues**

**Reporting Year:**

- No reportable issues arose this reporting year

**4. KEY RESEARCH ACCOMPLISHMENTS:**

**A. Regulatory Amendment Submissions, Continuing Reviews, and Protocol Modifications**

We submitted and received approval for our annual continuing review to our local IRB. Also, we submitted and received approval for a non-essential personnel protocol amendment.

**B. Study Devices and Equipment**

**Reporting Quarter/Year:**

- All left-over plasma was stored in our own -80 degree freezers and used for various testing including the efficacy of expired plasma in resuscitation in vitro. Once the units have expired they were properly discarded.

**C. Data Management**

- Publication in Lancet summarizing study findings

## **D. Other Accomplishments**

### **Reporting Quarter/Year**

We have optimized our proteomic methods to ensure maximum proteome coverage when analyzing plasma samples from the COMBAT study. We have partnered with Ceres Nanosciences to develop analytical methods that utilize their proprietary nanotrap technology to enrich for low level proteins, improving proteome coverage when analyzing samples by our optimized liquid chromatography tandem mass spectrometry method. We tested a magnetic based particle for proteome enrichment to facilitate automated sample preparation. It has been found that the magnetic particles exhibit a unique selectivity when compared to the standard microparticles. Some proteins of interest are lost in the conversion including integrins. Overall, the magnetic particles exhibit improved analysis over non-fractionated plasma analysis but we have decided to move forward with a protocol that utilizes a 96 well plate and a positive pressure manifold for sample preparation.

Analysis of ten patients' samples at all time points collected have been performed using LC-MS/MS data acquisition and a dozen samples using the nanotrap method. This dataset of 120 samples is being processed and will be used to inform analysis of the next batch of 400 samples which are being run in the coming month. We have been using these datasets to develop and evaluate data analysis pipelines for time-course analysis for longitudinal proteome and metabolite data.

- Several journal articles were published (see Section 6).

- **CONCLUSION:**

Publication in Lancet summarizing study findings

## **5. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:**

See attachment.

## **6. INVENTIONS, PATENTS AND LICENSES:** Nothing to report.

## **7. REPORTABLE OUTCOMES:**

### **Reporting Year:**

- Publication in Lancet summarizing study findings
- We continue to learn valuable information from our various proteomics and metabolomics tests.

## **8. OTHER ACHIEVEMENTS:** Nothing to report

## **9. REFERENCES:** Not applicable

## **10. APPENDICES:** See attached

- a. Feedback letters from the IRB
  - i. Continuing Review (CRV-006-1) 03.14.2019
  - ii. Amendment (PAM 022-1) 03.14.2019

## List of COMBAT trial related presentations and publications – 2018

### Publications/In press:

1. Stettler GR, Moore EE, Moore HB, Nunns GR, Silliman CC, Banerjee A, Sauaia A. Redefining Post Injury Fibrinolysis Phenotypes Using Two Viscoelastic Assays. *J Trauma Acute Care Surg.* 2018 Dec 18. doi: 10.1097/TA.0000000000002165. [Epub ahead of print] PubMed PMID: 30562328.
2. Stettler GR, Sumislawski JJ, Moore EE, Nunns GR, Kornblith LZ, Conroy AS, Callcut RA, Silliman CC, Banerjee A, Cohen MJ, Sauaia A. Citrated kaolin thrombelastography (TEG) thresholds for goal-directed therapy in injured patients receiving massive transfusion. *J Trauma Acute Care Surg.* 2018 Oct;85(4):734-740. doi: 10.1097/TA.0000000000002037. PubMed PMID: 30059456; PubMed Central PMCID: PMC6158094.
3. Moore HB, Moore EE, Chapman MP, McVaney K, Bryskiewicz G, Blechar R, Chin T, Burlew CC, Pieracci F, West FB, Fleming CD, Ghasabyan A, Chandler J, Silliman CC, Banerjee A, Sauaia A. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet.* 2018 Jul 28;392(10144):283-291. doi: 10.1016/S0140-6736(18)31553-8. Epub 2018 Jul 20. PubMed PMID: 30032977; PubMed Central PMCID: PMC6284829.
4. Nunns GR, Moore EE, Stettler GR, Moore HB, Ghasabyan A, Cohen M, Huebner BR, Silliman CC, Banerjee A, Sauaia A. Empiric transfusion strategies during life-threatening hemorrhage. *Surgery.* 2018 Aug;164(2):306-311. doi: 10.1016/j.surg.2018.02.024. Epub 2018 Apr 27. PubMed PMID: 29709368; PubMed Central PMCID: PMC6056322.
5. Stettler GR, Moore EE, Nunns GR, Chandler J, Peltz E, Silliman CC, Banerjee A, Sauaia A. Rotational thromboelastometry thresholds for patients at risk for massive transfusion. *J Surg Res.* 2018 Aug;228:154-159. doi: 10.1016/j.jss.2018.03.027. Epub 2018 Apr 11. PubMed PMID: 29907206; PubMed Central PMCID: PMC6039387.
6. Samuels JM, Moore EE, Silliman CC, Banerjee A, Cohen MJ, Ghasabyan A, Chandler J, Coleman JR, Sauaia A. Severe traumatic brain injury is associated with a unique coagulopathy phenotype *J Trauma Acute Care Surg.* 2018 Dec 26. doi: 10.1097/TA.0000000000002173.
7. Coleman JR, Moore EE, Samuels JM, Nunns GR, Stettler GR, Ryon J, Moore HB, Ghasabyan A, Chandler J, Banerjee A, Silliman CC, Sauaia A. Antifibrinolytics Are Associated With Robust and Prolonged Fibrinolysis Shutdown. Submitted to *Journal of Trauma and Acute Care Surgery.*

8. Coleman JR, Moore EE, Samuels JM, Cohen MJ, Sauaia A, Sumislawski JJ, Ghasabyan A, Chandler JG, Banerjee A, Silliman CC, Peltz ED. Trauma resuscitation considerations: sex matters. *Journal of the American College of Surgeons*;2018: In press.
9. Coleman JR, Moore EE, Chapman MP, Banerjee A, Silliman CC, Ghasabyan A, Chandler J, Samuels JM, Sauaia A. Rapid TEG efficiently guides hemostatic resuscitation in trauma patients. *Journal of Surgery*. 2018;164(3):489-493.

Presentations:

- a. Coleman JR, Moore EE, Samuels JM, Nunns GR, Stettler GR, Ryon J, Moore HB, Ghasabyan A, Chandler J, Banerjee A, Silliman CC, Sauaia A. Antifibrinolytics Are Associated With Robust and Prolonged Fibrinolysis Shutdown. American Association of the Surgery of Trauma/World Trauma Congress. San Diego, CA. September 28th, 2018. \*2nd Place Winner in Critical Care Resident Competition.
- b. Coleman JR, Moore EE, Butenas S, Olson A, Cohen MJ, Colvis A, Samuels JM, Ghasabyan A, Chandler J, Sauaia A, Banerjee A, Silliman CC. Prothrombin Time/International Normalized Ratio and Thrombelastography Discordances in Trauma Patients: an Examination of Correlation with Factor Levels and Thrombin Generation. American College of Surgeons Committee on Trauma State Resident Paper Competition. Colorado Springs, Colorado. August 24th, 2018. \*Winner of Basic Science Category in State Resident Competition.
- c. Coleman JR, Moore EE, Peltz ED, Samuels JM, Cohen MJ, Sumislawski JJ, Ghasabyan A, Chandler JG, Banerjee A, Sauaia A & Silliman CC. Sex Dimorphisms Following Trauma: Female Sex Confers a Hypercoagulable State and Survival Advantage. University of Colorado Department of Surgery Research Symposium. Denver, Colorado. May 21st, 2018. \*Winner of The Frederick L. Grover Award in Clinical Science



---

University of Colorado Hospital | Denver Health Medical Center | Colorado Prevention Center | Children's Hospital  
Colorado | Denver Health and Hospital Authority | VA Eastern Colorado Health Care System (Denver VAMC)

---

## Certificate of Approval

14-Mar-2019

**Title:** Control of Major Bleeding After Trauma (COMBAT): A prospective, randomized comparison of fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid

**Subject:** COMIRB Protocol 12-1349 Continuing Review

**Investigator:** Ernest Moore

**Sponsor(s):** Department of Defense~

**Effective Date:** 07-Mar-2019

**Expiration Date:** 06-Mar-2020

**Expedited Category:** 8

**Submission ID:** CRV006-1

---

### **SUBMISSION DESCRIPTION:**

Data Analysis. PAM022-1 reviewed concurrently.

---

**This study continues to be reviewed and approved under the “Pre-2018 Requirements” of the Federal Policy for the Protection of Human Subjects.**

Your COMIRB Continuing Review submission CRV006-1 has been APPROVED until the expiration date listed above. The investigator will need to submit this research for Continuing Review at least 30 days prior to the expiration date. If a study's approval expires, investigators must stop all research activities immediately (including data analysis) and contact the COMIRB office for guidance.

You are required to submit changes to your research for approval prior to implementing those changes. You are required to report unanticipated problems and serious or continuing noncompliance to COMIRB. When your research is complete you must report the study closure to COMIRB.

Your responsibilities as Principal Investigator are posted here:

<http://www.ucdenver.edu/research/Research%20Administration%20Documents/Responsibilities-of-Investigators.docx>

**REVIEW DETAILS**– Please read carefully:

APPROVED:

Enrollment is complete and participants have completed all research related interventions and long-term follow-up. Research activities are limited to data analysis only. No additional risks have been identified. The continuing review is

approved by chair review.

The submission included an extensive list of COMBAT Trial related publications and presentations for 2018. Prior to the next continuing review please develop and submit the proposed community disclosure plan to COMIRB for review to begin the process of informing the community of study results. Please refer to the FDA's guidance on Exception from Informed Consent Requirements for Emergency Research for detailed information on public disclosure requirements.

Continuing Review CRV006-1 was reviewed and approved concurrently with Amendment PAM022-1. The personnel form was reviewed with this continuing review. The new version of this document is approved with the associated amendment PAM022-1.

The following documents have been reviewed as part of this approval:

1. Continuing Review form.
2. Application for Protocol Review, Version Date: Mar 16, 2017.
3. Personnel form (revised and approved in PAM022).
4. Protocol: Control Of Major Bleeding After Trauma (COMBAT): A prospective, randomized comparison of fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid, Version Date: 12/27/2016.
5. List of COMBAT trial related presentations and publications- 2018.
6. List of Withdrawals.
7. Consent with HIPAA authorization form (English), Version Date: 02/07/2017, Version #: 10.
8. Consent with HIPAA authorization form (Spanish), Version Date: 2/12/2016, Version #: 8.

The consent forms are not approved for use at this time because the study is closed to enrollment. If red-line changes were made, the tracked changes and clean versions have been uploaded into eRA (InfoEd). If the PI disagrees with these changes, submit a change form to COMIRB with the revised documents.

**Click here to your submission:** [Submission Page](#)

Study personnel are approved to conduct the research as described in the above documents approved by COMIRB

Information on how to submit changes (amendments) to your study, reports of unanticipated problems, and request for study closure to COMIRB can be found on the COMIRB website  
<http://www.ucdenver.edu/research/comirb/submissions/Pages/default.aspx>

**For the duration of this research the investigator must:**

- Submit any change in the research design, investigator, and any new or changed study documents (including new/changed consent forms, questionnaires, advertisements, etc.) to COMIRB and receive approval before implementing the changes
- Use only a copy of the COMIRB-approved, stamped Consent and/or Assent Form. The investigator bears the responsibility for obtaining Informed Consent from all subjects as required by COMIRB prior to the start of study procedures. COMIRB REQUIRES that the subject be given a copy of the consent and/or assent form after it is signed.
- Inform COMIRB immediately of any Unanticipated Problems that are unexpected and related to the study in accordance with COMIRB Policies and Procedures.
- Maintain approval for the research by submitting the continuing review for re-approval at least 45 days prior to the expiration date.
- Remain actively engaged in the conduct of the research. The investigator must ensure that all enrolled participants are appropriate for the study prior to study procedures beginning.

**As part of this review it was determined that for this research:**

1. Risks to subjects are minimized.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
3. Selection of subjects is equitable.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative in accordance with, and to the extent required by, §46.116.
5. Informed consent will be appropriately documented in accordance with, and to the extent required by, §46.117.
6. The research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. Appropriate safeguards are in place to protect potentially vulnerable populations from coercion and undue influence.

Please reply to the email containing this letter, contact the COMIRB Help Desk at [COMIRB@ucdenver.edu](mailto:COMIRB@ucdenver.edu) or call 303-724-1055 if you have questions or concerns.

Sincerely,

UCD Panel A



---

University of Colorado Hospital | Denver Health Medical Center | Colorado Prevention Center | Children's Hospital  
Colorado | Denver Health and Hospital Authority | VA Eastern Colorado Health Care System (Denver VAMC)

---

## Amendment Approval

14-Mar-2019

**Title:** Control of Major Bleeding After Trauma (COMBAT): A prospective, randomized comparison of fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid

**Subject:** COMIRB Protocol 12-1349 Amendment

**Investigator:** Ernest Moore

**Sponsor(s):** Department of Defense~

**Approval Date:** 07-Mar-2019

**Submission ID:** PAM022-1

---

### REQUESTED CHANGES:

Changes to Personnel- Personnel form only. Reviewed concurrently with CRV006-1.

We are removing the personnel no longer involved with the study.

Remove:

Choi, Young  
Einersen, Peter  
Fleming, Courtney  
Huebner, Benjamin  
Jarvis, Stephanie  
Leopold, David  
McGuffin, Samuel  
Nunns, Geoffrey  
Shepherd-Singh, Raymond  
Stettler, Gregory

---

**REVIEW DETAILS**– Please read carefully:

APPROVED:

PAM022 was submitted concurrently with the continuing review. The amendment requests the removal of personnel and includes a revised Personnel Form. The amendment is approved by chair review.

The following documents have been reviewed as part of this approval:

1. Change form, Date: 02/05/2019.
2. Personnel form, 07-Feb-2019.
3. Cover letter, February 05th, 2019.

COMIRB only stamps the approved versions of consent documents and local advertisements in the top right hand corner. Approved copies of the study documents are available for download via eRA(InfoEd).

If red-line changes were made, the tracked changes and clean versions have been uploaded into eRA (InfoEd). If the PI disagrees with these changes, submit a change form to COMIRB with the revised documents.

**Click here to your submission:** [Submission Page](#)

Please reply to the email containing this letter, contact the COMIRB Help Desk at [COMIRB@ucdenver.edu](mailto:COMIRB@ucdenver.edu) or call 303-724-1055 if you have questions or concerns.

Sincerely,

UCD Panel A