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

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

PRINCIPAL INVESTIGATOR: **Ernest E. Moore**

RECIPIENT: **University of Colorado Denver**

REPORT DATE: **March 2020**

TYPE OF REPORT: **Annual Report**

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

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

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W81XWH-12-2-0028

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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8. PERFORMING ORGANIZATION REPORT NUMBER

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

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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

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.

15. SUBJECT TERMS

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

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	14	19b. TELEPHONE NUMBER *(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

1. INTRODUCTION:

This report includes April 1st, 2019 – March 31st, 2020.

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)≤70mmHg or 71-90mmHg with HR≥108bpm, 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

Term	**# of Patients Enrolled**	**# of Samples Collected**
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 continue using -30C and -80C freezers for our specimen storage needs. All Plasmatherm devices are currently stored in the Surgical Research Lab at Denver Health. All high capacity batteries and converters are stored at Paramedic storage facility.

F. Problems/Issues

None.

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 a protocol amendment with proposed Community Disclosure plan to notify the public about the study results per CFR 50.24. The full board review is currently pending (see the deferral letter attached).

B. Study Devices and Equipment

Reporting Quarter/Year:

- None

C. Data Management

- Publication in JAMA summarizing study findings.

D. Other Accomplishments

Reporting Quarter/Year

We have had very good analytical results with the Ceres nanoparticles and have established a protocol for running samples. This protocol will be used and to move forward we identified the new timsTOF mass spectrometer with data independent acquisition with Parallel accumulation – serial fragmentation DIA-PASEF capabilities to as a superior platform for acquiring protein identifications for this study.

We worked to acquire this system and it was installed at the beginning of the year. In addition, we purchased a new liquid chromatography system (both purchased with University funds). These system have been installed and tested and are not performing optimally due to instability of the nano-spray ion source. We are working with the vendor daily to resolve these issues. We are close to a solution as we have seen an increase in performance from 25% success rate to ~80%.The success rate needs to be 99% before we finalize the running of samples for this project.

Analysis of ten patients' samples at all time points collected have been performed using the older LC-MS/MS data acquisition and a dozen samples using the nanotrap method. This dataset of 120 samples has been processed and is being used to inform analysis of the next batch of 400 samples. 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 5).

- **CONCLUSION:**

Publication in JAMA 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 JAMA summarizing study findings
- Relationships between metabolites and the clinical endpoints are yielding hypotheses that are being tested.
- Proteomic analysis is revealing patient specific trajectories have similar features based on injury type and severity that we are beginning to explore.

8. OTHER ACHIEVEMENTS: Nothing to report

9. REFERENCES: Not applicable

10. APPENDICES: See attached

a. Feedback letters from the IRB
    i. Continuing Review (CRV-007-1) 03.06.2020
    ii. Deferral to full board review (PAM 023-1) 03.06.2020

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UCD Anschutz Medical Campus | UCD Downtown Denver Campus | University of Colorado Health | Denver Health and Hospitals | Colorado Prevention Center | Children's Hospital Colorado | Colorado School of Mines | VA Eastern Colorado Health Care System

Certificate of Approval

06-Mar-2020

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:	06-Mar-2020
Expiration Date:	05-Mar-2021
Expedited Category:	8

Submission ID: CRV007-1

SUBMISSION DESCRIPTION:

Data Analysis. PAM023-1 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 CRV007-1 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: This research requires continuing review because it is subject to FDA regulations and it is funded by DoD.

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 the review period. At the previous continuing review (CRV006), the reviewer had requested that the study team develop and submit the proposed community disclosure plan to COMIRB for review to begin the process of informing the community of study results. The reviewer noted that this was submitted in PAM023 concurrently with this continuing review.

PAM023 provides the Community Consultation and Public Disclosure Plan that is proposed to meet the FDA's guidance on Exception from Informed Consent Requirements for Emergency Research. Additionally, personnel changes were requested. Defer to full board for review and approval of this plan.

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, 05-Mar-2020.
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- 2020.
6. List of Withdrawals, no date.
7. Cover letter, March 6th, 2020.
8. Consent with HIPAA authorization form (English), Version Date: 02/07/2017, Version #: 10.
9. Consent with HIPAA authorization form (Spanish), Version Date: 2/12/2016, Version #: 8.

The consent forms are not stamped/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 or call 303-724-1055 if you have questions or concerns.

Sincerely,

UCD Panel A

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Amendment Deferred

06-Mar-2020

Investigator:	Ernest Moore
Sponsor(s):	Department of Defense~
Subject:	COMIRB Protocol 12-1349 Amendment
Review Date:	06-Mar-2020
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

Submission ID: PAM023-1

REQUESTED CHANGES:

Changes to Personnel and submission of plan for after study completion Public Disclosure. Reviewed concurrently with CRV007-1.

Remove: Kirk Hansen, PhD, co-investigator
Anirban Banerjee, PhD, co-investigator
Steven Moulton, MD, co-investigator
Jason Samuels, MD, co-investigator
Joshua Ryon, RAII [DHH]
Megan Swope, PRA

PERSONNEL CHANGES: We are removing the personnel no longer involved with the study. Also, we are submitting a draft plan for after study completion Public Disclosure.

Your COMIRB Amendment submission PAM023-1 has been DEFERRED for review by the full board.

Stipulated changes to certain documents or clarifications may be needed prior to full board review. These changes would be described in the REVIEW DETAILS section below.

If changes or clarifications are not listed, your submission will be reviewed by the full board as soon as possible. If changes or clarifications are stipulated below, your submission will be scheduled for full board review when those stipulations are addressed. If the changes or clarifications are not received within 120 days, the submission will be WITHDRAWN. No research activities pertaining to this submission may begin until final approval is received.

Click here for instructions on how to respond to these stipulated changes via the eRA(InfoEd) website, if changes or clarifications are requested.

REVIEW DETAILS:

DEFERRED TO FULL BOARD:

At the previous continuing review (CRV006), the reviewer had requested that the study team develop and submit the proposed community disclosure plan to COMIRB for review to begin the process of informing the community of study results.

PAM023 provides the Community Consultation and Public Disclosure Plan that is proposed to meet the FDA's guidance on Exception from Informed Consent Requirements for Emergency Research. Additionally, personnel changes were requested. Defer to full board for review and approval of this plan.

**No action is required by the PI at this time. This amendment will be assigned to the next available Panel A meeting agenda. **

Sincerely,

UCD Panel A

W81XWH-12-2-0028
PI: Ernest E. Moore

Publications:

Pusateri AE, Moore EE, Moore HB, Le TD, Guyette FX, Chapman MP, Sauaia A, Ghasabyan A, Chandler J, McVaney K, Brown JB, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Witham WR, Putnam AT, Sperry JL. Association of Prehospital Plasma Transfusion With Survival in Trauma Patients With Hemorrhagic Shock When Transport Times Are Longer Than 20 Minutes: A Post Hoc Analysis of the PAMPer and COMBAT Clinical Trials. JAMA Surg. 2019 Dec 18:e195085. doi:

Pusateri AE, Butler FK, Shackelford SA, Sperry JL, Moore EE, Cap AP, Taylor AL, Homer MJ, Hoots WK, Weiskopf RB, Davis MR. The need for dried plasma – a national issue. Transfusion. 2019 Apr;59(S2):1587-1592. doi: 10.1111/trf.15261. PMID: 30980738

Reitz KM1, Moore HB, Guyette FX, Sauaia A, Pusateri AE, Moore EE, Hassoune A, Chapman MP, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Brown JB, Zuckerbraun BS, Neal MD, Yazer MH, Sperry JL. Prehospital plasma in injured patients is associated with survival principally in blunt injury results from two randomized prehospital plasma trials. Information Journal of Trauma and

Anto VP, Guyette FX, Brown J, Daley B, Miller R, Harbrecht B, Claridge J, Phelan H, Neal M, Forsythe R, Zuckerbraun B, Sperry J; and The PAMPer study group. Severity of haemorrhage and the survival benefit associated with plasma: results from a randomised prehospital plasma trial. J Trauma Acute Care Surg. 2020; 88: 141-147 doi: 10.1097/TA.0000000000002530. PMID: 31688793

Moore HB, Moore EE, Neal MD, Sheppard FR, Kornblith LZ, Draxler DF, Walsh M, Medcalf RL, Cohen MJ, Cotton BA, Thomas SG, Leeper CM, Gaines BA, Sauaia A. Fibrinolysis Shutdown in Trauma: Historical Review and Clinical Implications. Anesth Analg. 2019 Sep;129(3):762-773. doi:

Barrett CD, Moore HB, Kong YW, Chapman MP, Sriram G, Lim D, Moore EE, Yaffe MB. Tranexamic acid mediates proinflammatory and anti-inflammatory signaling via complement C5a regulation in a plasminogen activator-dependent manner. J Trauma Acute Care Surg. 2019 Jan;86(1):101-107. doi:

Presentations:

Coleman JR, Moore EE, Kelher MR, Cohen MJ, Ghasabyan A, Chandler J, Samuels JM, Jones K, Banerjee A, Silliman CC. Elucidating the Molecular Mechanisms of Fibrinolytic Shutdown after Severe Injury: the Role of Thrombin Activatable Fibrinolysis Inhibitor. American College of Surgeons Clinical

Coleman JR, Moore EE, Butenas S, Olson A, Cohen MJ, Colvis A, Samuels JM, Ghasabyan A, Chandler J, Sauaia A, Silliman CC. PT/INR is a strong biomarker of injury severity but does not indicate critical coagulation factor deficiency: an examination of PT/INR and thrombelastography discordances.

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 National