

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, MD**

CONTRACTING ORGANIZATION: **University of Colorado Denver
Aurora, CO 80045**

REPORT DATE: **May 2016**

TYPE OF REPORT: **Annual Report**

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

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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.						
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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 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.

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1. INTRODUCTION:

This report includes the quarter from January 1, 2016 – March 31, 2016 and the reporting year from July 1, 2015 – March 31, 2016.

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) ≤ 70 mmHg or 71-90mmHg with HR ≥ 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 made minor adjustments to our blood sampling and processing methodologies and processes in order to make the most of our time and resources.

B. Patient Enrollment and Sample Procurement

Reporting Quarter: This quarter, we enrolled 17 patients and collected 1,936 plasma samples. See Table 1 below.

Reporting Year: This reporting year, which is shorter than most other years, we enrolled 41 patients and collected 4,502 plasma samples. See Table 1 below.

Table 1: Summary by Quarter, Year, and Total

Term	# of Patients Enrolled	# of Samples Collected
1/1/16 – 3/31/16	17	1936
10/1/15 – 12/31/15	10	1391
7/1/15 – 9/30/15	14	1175
Total for Reporting Year	41	4502
Total Since Study Start	98	11808

During this reporting year, we sent 405 samples to the Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC). We also sent 95 samples to the Children's Hospital of Colorado for clotting analysis during the reporting year. A total of 360 samples were processed for meso-scale analysis using V-PLEX Plus Human Biomarker kits this reporting year.

C. Unanticipated Problems and Patient Withdrawals

Reporting Quarter: Four unanticipated problems (UAPs) were submitted to the local IRB. Two UAPs were submitted because patients were enrolled without meeting inclusion criteria; one UAP was submitted for the enrollment of a minor patient; and one UAP was submitted because a patient was discharged before consent could be obtained. All appropriate regulatory agencies were notified, and our team continues to work with paramedic staff to ensure appropriate measures are taken in the future, should similar situations arise. Detailed information on each situation can be found on the letters from the IRB, attached to this report.

Reporting Year: Six UAPs arose this reporting year, including four during this quarter (see above). We communicated with the COMIRB immediately after encountering each problem, and we submitted all documentation to each appropriate regulatory agency in a timely manner.

D. Paramedic Training and Continuing Education

Reporting Quarter: During the January-March 2016 quarter, 16 paramedics were hired by the Denver Paramedic Division. Each new hire was trained for patient enrollment, study procedures, and other key information by a member of our study team.

Reporting Year: This reporting year, our team trained 30 new paramedics and EMTs. Since the study began, we have trained approximately 317 paramedics and EMTs. Throughout the reporting year, our study team is continuously trained on new procedures and consistently adapts to various situations as they arise.

We plan to hold a reception ceremony later this month (April 2016) for paramedics to thank them for the hard work throughout the past year of the study enrollment. We will use this gathering as a time to provide continuing education with the study procedures and materials, and we will be available to answer any questions the paramedics may have.

E. Study Devices and Equipment

Quarterly maintenance continues to be performed on all our team's freezers by the contracted company, Tolin Mechanical. These freezers store FFP, cooler bottles, and banked plasma samples. Daily quality control checks are performed on the freezers to ensure study materials are maintained properly.

Preventative maintenance continues to be performed regularly on our TEG machines by representatives from Haemonetics.

F. Problems/Issues

During the past year, we have encountered various logistical problems with study procedures and equipment. Each of these is addressed on a regular basis and in a timely manner, as described below:

Reporting Quarter:

- We found a unit of plasma with a leak in it this quarter. We took immediate action by removing the unit from service. We decided to proactively check all units as a preventative measure and manually inspected every plasma unit to check for leaks or damages; all inspections were inconsequential.
- Several of our TEG machines had issues with their Quality Control tests this quarter. We took immediate action and had a Haemonetics technician come and repair any malfunctioning units.
- One of our study freezers holding bottles began progressively warming. After moving the bottles from the unit to a back-up freezer, we thawed the unit at the recommendation of our service technicians (contracted with Tolin) and have not had any further issues. We will continue to defrost freezers on a regular basis (see section 4B below).
- One of our centrifuges in the lab had a broken motor. This was quickly replaced by service technicians.

Reporting Year:

- We continue working to resolve the issue where some of our Plasmatherms had illegible faceplate screens, likely due to humidity. Since last summer, the number of units with this issue has decreased (we reported this in the previous annual report)
- Several inverters used in ambulances have malfunctioned and become inoperable. We have used Denver Health’s Biomedical Services Department for reconciliation of these units.
- Various logistical problems with study procedures and equipment are being addressed on a regular basis.
- In certain cases, the follow-up of patients presents a challenge due to instances such as an absence of a permanent address, a disconnected telephone, etc.
- Miscellaneous electrical issues, which are not study specific, continue to cause problems within ambulances. As these electrical problems arise, they are dealt with in a timely fashion. We are actively mitigating these issues with the company subcontracted by the Denver Health Paramedic Division to repair electrical issues with ambulances.

4. KEY RESEARCH ACCOMPLISHMENTS:

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

This reporting year, we submitted five amendments to our local IRB to further refine our study and to adapt to new situations regarding patient enrollment, data collection, and sample procurement. We submitted our annual continuing review to our local IRB as well, and it is scheduled to be reviewed this month (April 2016).

We also submitted an annual report to the FDA concerning our IND as well as an amendment. The amendment aims to add a non-invasive device to our study that will collect waveform data on study participants, in an effort to correlate it with blood transfusion predictions. This amendment was approved by the FDA, and we are in the process of submitting it to the HRPO and then to our local IRB. The amendment, as submitted to the FDA, is attached to this report along with their approval letter. See Table 2 for more details.

It should also be noted that we received an audit by the University of Colorado's Office of Regulatory Compliance in November 2015. This review was overly positive, and the report was attached to the 13th Quarterly Report. We have received no other audits to date.

Table 2: Regulatory Submissions

Quarter	Submission Type	Reason/Notes
1/1/16 – 3/31/16 (feedback letters from the IRB for this quarter's submission are included in this report)	Amendment	Data sharing agreement with TACTIC and addition of an information sheet for minor patients enrolled
	Amendment	Spanish consent addition and change to study personnel
	Amendment to IND	Addition of non-invasive device to collect waveform data on study participants (pending HRPO approval and IRB approval; FDA approval granted)
	Continuing Review	Scheduled for review this April
10/1/15 – 12/31/15	Amendment	Change to study personnel
	Amendment (withdrawn)	Addition of non-invasive device and data sharing with TACTIC (this was withdrawn and submitted at a later time)
7/1/15 – 9/30/15	Amendment	Change to study personnel
	FDA IND Annual Report	Annual report to the FDA on study status (this was submitted with the 12 th Quarterly Technical Progress Report)

B. Study Devices and Equipment

Reporting Quarter:

- Within the last few months, our Plasmatherms have had an increase in pump and power supply failures. This is likely due to the fact that the devices are running continuously, so as to be ready for possible enrollment at any time. This, combined with heat, vibration, and dust, puts strain on the system, making an increase in mechanical failures with time to be expected. These issues come with additional cost and labor requirements but are understood and have not affected enrollment capability.
- Preventative Maintenance was performed for all TEG machines in our lab this quarter. Following the suggestion of the service technician, we revised our weekly Quality Control procedures for TEG machine maintenance.
- The pipettes in our lab were calibrated to ensure proper measurements
- All of our experimental plasma unit cassettes were audited to check for any potential leaks or damage.
- We devised a plan to defrost all of 5 our Helmer freezers on a rotating basis. This plan will result in a complete defrost of each Helmer freezer every 5 months on a rotating basis in order to perform preventative maintenance and to ensure proper functioning of all study equipment freezers.

- Tolin continued to perform quarterly maintenance checks on freezer units.
- We decided to increase the total amount of circulating plasma and placebo units in service to 40 (previously was 32) in order to increase the amount of time each unit is in the freezer as a preventative measure. This will be especially beneficial during the summer months. The ratio of plasma to placebo remains one-to-one.

Reporting Year

- We have encountered a significantly reduced number of freezer problems since switching to Helmer-brand freezers at the end of June 2015
- A log was implemented in the Paramedic Garage so vehicle service technicians can document communication of any study equipment or ambulance issues with our study team.
- We continue to perform twice-daily inventory of the plasma freezer in the paramedic garage to ensure continuous quality control of all experiment and control units. This method has proven to be effective this past year in reducing the time a unit is away from the freezer.
- We revised our standard-operating procedure that documents the workflow of vehicle service technicians (VSTs) who build and break-down study coolers each shift in order to ensure consistency and reliability and to reflect changes made by their supervisors.
- We began implementing a new coagulopathy scoring system for our study patients in an effort to better align with the Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC).

C. Data Management

- The REDCap data collection system is continuously being revised and improved to assist our team in collecting timely and accurate data.
- This month, Denver Health is transitioning to the Epic Medical Records system. Our entire research team has been involved in training courses and preparation for this change. We anticipate complications with data procurement at the beginning of the transition, but we are prepared for the change and are working to ensure a smooth adjustment in our workflow.

D. Other Accomplishments

Reporting Quarter

- A renewal of the paramedic waiver for plasma transfusions in the field was approved by the Emergency Medical Practice Advisory Council (EMPAC) through the end of the study.
- We received a “no-cost extension” through April 2017 from the Department of Defense to extend patient enrollment obligations.

Reporting Year

- Several journal articles were published (see Section 6).
- We installed equipment in several new ambulances at Denver Health.
- We hired and trained two new research assistants this reporting year (12th Quarterly Report) and are in the process of hiring two additional research assistants to replace the impending departure of two current research assistants this summer.

5. CONCLUSION:

We continue to enroll patients in the study, and our team is constantly adapting. We anticipate additional problems and/or issues to arise, but we plan to address them in a timely fashion. Over the next few weeks, we will likely enroll patient 100, at which point we will conduct our second interim analysis, as required by the DSMB. We will also submit our third IND Annual Report to the FDA in September 2016.

We plan on training two new research assistants in the coming months to replace two current research assistants who are departing the lab this summer. We will also be providing opportunities to paramedics for continuing education and study-refresher courses.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

- Chapman, MP, Moore, EE, Moore, HB, Gonzalez, E, Chin, TL, Silliman, CC, and Banerjee, A: Tranexamic Acid Inhibited Thromboelastography is a More Sensitive and Rapid Predictor of Hyperfibrinolytic Hemorrhage in Trauma than Conventional Viscoelastic Hemostatic Assays (Presented at the Shock Society, Charlotte, NC, June 2014). *Shock*. 41: 93, 2014
- Moore, HB, Moore, EE, and Gonzalez, E: Mortality and Ratio of Blood Products used in Patients with Severe Trauma. *JAMA*. 313: 2077, 2015
- Chin TL, Moore EE, Moore HB, et al. A principal component analysis of post injury viscoelastic assays: clotting factor depletion versus fibrinolysis. *Surgery*;156:570-577. (Presented at the Society of University Surgeons, San Diego, CA, February 2014). *Surgery*.
- Moore, HB, Moore, EE, Gonzalez, E, Chapman, M, Sauaia, A, and Banerjee, A: Activated Clotting Time Predicts Early Post injury Blood Component Transfusion beyond Plasma (Presented at the Society of University Surgeons, San Diego, CA, February 2014). *Surgery*. 156: 564, 2014
- Gonzalez, E, Moore, EE, Moore, HB, Chapman, MP, Silliman, CC, and Banerjee, A: Alpha-enolase, A Glycolytic Enzyme Elevated in Hemorrhagic Shock, Potentiates Fibrinolysis, and is Reversible by Tranexamic Acid (Presented at the Shock Society, Charlotte, NC, June 2014). *Shock*. 41: 48, 2014
- Chapman, MP, Moore, EE, Moore, AB, Gonzalez, E, Gamboni, F, Chandler, JG, Ghasabyan, A, Chin, TL, Sauaia, A, Banerjee, A, and Silliman, CC: Overwhelming tPA Release, not PAI – 1 Degradation, is Responsible for Hyperfibrinolysis in Severely Injured Patients (Presented at the American Association for the Surgery of Trauma, San Francisco, CA, September, 2014). *J Trauma Acute Care Surg*. In Press
- Chapman, MP, Moore, EE, Moore, HB, Chin, TL, Gamboni, F, Banerjee, A, Sauaia, A, and Silliman, CC: Massive Plasminogen Activator Inhibitor-1 Upregulation and Suppressed Fibrinolysis is the Predominant Phenotype in Severely Injured Patients (Presented at the Surgical Forum at the American College of Surgeons, San Francisco, CA, October, 2014). *J Am Coll Surg*. 219: 46, 2014
- Chapman MP, Moore EE, Moore HB, et al. The Death Diamond: Rapid thrombelastography identifies lethal hyperfibrinolysis. *Journal of Trauma and Acute Care Surgery*;79:925-929. (Presented at the Western Trauma Association, Telluride, CO, March, 2015).
- Quinn, B, Gonzalez, E, Moore, EE, Moore, HB, Chapman, MP, Morton, AP, Sauaia, A, Banerjee, A, and Silliman, CC: Defining the Optimal Thrombelastography Assay to Detect

Fibrinolysis in Trauma Patients. (Presented at the Academic Surgical Congress, Las Vegas, NV, February 2015). J Surg Res. In Press

- Moore, HB, Moore, EE, Morton, AP, Gonzalez, E, Chapman, MP, Sauaia, A, Anderson, C, Banerjee, A, and Silliman, CC: Hemorrhagic Shock Stimulates Organ Tissue Release of tPA Independent of Disseminated Intravascular Coagulation (Presented at the Shock Society, Denver, CO, June 2015). Shock. 43: 101, 2015
- Chapman, MD, Moore, EE, Moore, HB, Gonzalez, E, Morton, AP, Silliman, CC, Sauaia, A, and Banerjee, A: Early TRAP Pathway Platelet Inhibition Predicts Coagulopathic Hemorrhage in Trauma (Presented at the Shock Society, Denver, CO, June 2015). Shock. 43: 37, 2015
- Moore HB, Moore EE, Liras IN, et al. Acute Fibrinolysis Shutdown after Injury Occurs Frequently and Increases Mortality: A Multicenter Evaluation of 2,540 Severely Injured Patients. Journal of the American College of Surgeons;222:347-355. (Presented at the Southern Surgical Association, Hot Springs, VA, December 2015). J Am Coll Surg.
- Moore, HB, Moore, EE, Gonzalez, E, Chapman, MP, Morton, AP, Slaughter, A, Banerjee, A, and Silliman, CC. The Unrecognized Role of Platelet Dysfunction in Trauma Induced Hyperfibrinolysis. (Presented at the Surgical Forum of the American College of Surgeons, Chicago, IL, October 2015). J Am Coll Surg. 221: 168, 2015
- Moore, EE, Moore, HB, Gonzalez, E, Sauaia, A, Banerjee, A, and Silliman, CC. Rationale for the Selective Administration of Tranexamic Acid to Inhibit-Fibrinolysis in the Injured Patient. (Presented at Trauma Hemostasis and Oxygenation Research, Bergen, Norway, June 2015). Transfusion. In Press

7. INVENTIONS, PATENTS AND LICENSES: Nothing to report.

8. REPORTABLE OUTCOMES:

Reporting Quarter:

- We began the regulatory processes for implementing a non-invasive device that measures waveform data into our study (see above).
- We modified and finalized our agreements with TACTIC.

Reporting Year:

- The entire Denver Health ambulance fleet is equipped with Plasmatherm plasma-thawing devices. The devices are fully operational and are regularly maintained.
- We continue to learn valuable information from our various proteomics and metabolomics tests, meso-scale analysis tests, and coagulation factors tests.

9. OTHER ACHIEVEMENTS: Nothing to report

10. REFERENCES: Not applicable

11. APPENDICES: See attached

- a. Feedback letters from the IRB
 - i. UAP008
 - ii. UAP009
 - iii. UAP010 *Pending final approval notes-see deferral*
 - iv. UAP011 *Pending final approval notes-see deferral*
 - v. Amendment 02.12.2016
 - vi. Continuing Review 2016 *Pending receipt of letter—no attachment*

- vii. Amendment 03.04.2016 *Pending receipt of letter—no attachment*
- b. FDA IND Approval Letter



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University of Colorado Denver
Colorado Prevention Center

COMIRB Review Feedback

22-Jan-2016

Investigator: Ernest Moore
Sponsor(s): Department of Defense~
Subject: COMIRB Protocol 12-1349 Unanticipated Problem
Effective Date: 1/15/2016
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: UAP008-2

Submission Description:

UAP008-2: Response to Deferral to full board.

UAP008-1: Initial submission of non-compliance/protocol deviation involving enrolling a vulnerable population not approved by COMIRB and failure to obtain consent/HIPAA for local subject C-084.

On 1/2/16 at around 17:05, paramedics responded to a patient who cut his hand with a saw. The patient had extensive bleeding and met selection criteria for the COMBAT Study. The patient was randomized to the control arm (normal saline) by the paramedics. Following his Hour 6 blood draw and before his Hour 12 blood draw, the patient was discharged from the Emergency Department to jail. The patient was taken into custody after his admission to the hospital (presumably for the possession of an illegal substance) and discharged to jail before informed consent was obtained. Study personnel learned about the custody and discharge only post-factum, and no blood was drawn after the patient's custody status was known.

The study team made the following efforts to contact the patient to discuss the study enrollment and to obtain an informed consent - in order to reach the patient we contacted both Correctional Care Medical Facility (CCMF) at Denver Health and Denver County Jail 01/05/16. We were told that the patient bonded out on 01/04/16 and we were given the most current phone number and address for this patient. We made attempts on 5th, 6th and 7th of January to reach the patient by phone. All three times we got a busy signal and were not able to leave a message.

This case was discussed with IRB (Marty Schafer) over the phone on 01/07/16 and per her suggestion current UAP is being submitted.

PI assessment of risk:

This patient was randomized to the Control group and received normal saline prior to arrival, as all other non-study patients would do. No more blood was drawn after the study personnel became aware of the change in the patient's legal status. For the reasons outside of study personnel's control (explained in the narrative section) the patient was not informed about his study enrollment and wasn't given the opportunity to opt out.

Corrective Action Plan:

The study team made the following efforts to contact the patient to discuss the study enrollment and to obtain an informed consent - in

order to reach the patient we contacted both Correctional Care Medical Facility (CCMF) at Denver Health and Denver County Jail 01/05/16. We were told that the patient bonded out on 01/04/16 and we were given the most current phone number and address for this patient. We made attempts on 5th, 6th and 7th of January to reach the patient by phone. All three times we got a busy signal and were not able to leave a message.

Review Comments:

Unanticipated Problem:

COMIRB noted the Chair review and subsequent deferral to full board performed on 11-Jan-2016. The Chair deferred this unanticipated problem report to the full board in order to discuss the UAP involving enrollment of a prisoner subject in this study approved under 21 CFR 50.24, exception from informed consent requirements for emergency research.

This unanticipated problem report submission has been reviewed by the committee and the following determination has been made:

NOTED

The committee reviewed the submitted UAP, which reported the incident as non-compliance. The committee determined that the reported incident does not represent as non-compliance because the study is approved for continued enrollment of subjects who are taken into police custody after enrollment, while the study excludes any known prisoners at the time of enrollment. In addition, the committee noted the study team made a good-faith effort to contact and obtain consent from the subject after the subject was taken into police custody according to the consent process approved by the committee.

Committee issues and concerns:

1. Prior to the meeting, the committee asked the study team to clarify if family members of the subject involved in this report were contacted to locate the subject. The study team responded that they were unable to contact the family members while the subject was hospitalized and that the family members did not return the study team's calls. The committee found this response acceptable.
2. The committee noted that the study is approved for continued enrollment of subjects who are taken into police custody after enrollment, while the study excludes any known prisoners at the time of enrollment. The committee requested similar incidents to the one reported in this UAP be documented by the study team and reported at the time of continuing review. They do not require immediate reporting as a UAP.
3. The committee confirmed that the same principle for prisoner subjects stated above applies to pregnant subjects. The study excludes any known or apparent pregnant women at the time of enrollment; however, the study is approved for continued enrollment of pregnant subjects unless they object to continued participation. Please keep track of pregnant subjects and report them at the time of continuing review. No immediate reporting as a UAP is not necessary .

Please note that COMIRB will no longer be E-mailing approved documents. Stamped, approved documents can be retrieved in the eRA (InfoEd) system. [Please click here](#) to access instructions on finding these approved documents.

Sincerely,

UCD Panel A



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Veteran's Administration Medical Center
Children's Hospital Colorado
University of Colorado Denver
Colorado Prevention Center

COMIRB Review Feedback

01-Apr-2016

Investigator: Ernest Moore
Sponsor(s): Department of Defense~
Subject: COMIRB Protocol 12-1349 Unanticipated Problem
Effective Date: 03/25/2016
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: UAP009-2

Submission Description:

UAP009-2: Response to Deferral.

UAP009-1: Initial Report, Subject id#C-092, Non-compliance

On 03/01/16 around 15:00, paramedics responded to a 20's male patient with multiple gunshot wounds. The fire department arrived at the scene first and took a set of vitals prior to paramedic arrival. They read a systolic pressure of 88 mmHg with an unknown heart rate. After arrival, the paramedics assumed care of the patient and measured vital signs. This time, the systolic pressure was 92 mmHg with a heart rate of 128.

Inclusion criteria for the study requires vital signs of: systolic blood pressure less than 70 mmHg or a combination of systolic blood pressure 71-90 mmHg with a corresponding heart rate of 108 or greater.

There was a great deal of confusion on the scene due to the critically ill, bleeding patient and heavy police presence. It looks like the systolic pressure of 88 mmHg that was obtained by the Fire Department was erroneously combined with a heart rate of 128, which would, indeed, make this patient eligible for the study. The patient was randomized to the study arm (fresh frozen plasma) by the paramedics. The transfusion was started prior to the hospital arrival.

Upon hospital arrival, the study team took a report from the paramedics in the ED. The study team noticed the discrepancy in the set of vital signs that were used to screen and enroll the patient in the study. After verifying the information with the medics in-person and confirming that the set of vitals used to enroll the patient were outside of study selection criteria, the information was immediately relayed to the Surgery/Trauma attending physician leading patient care in ED. At this point, the decision was made to stop the plasma transfusion, as this patient did not meet study inclusion criteria. No further study related procedures (blood draw, etc.) were performed.

Study PI Dr. Moore was immediately notified and approved the on-call research team's decision. The event was promptly communicated to COMIRB on 03.02.2016.

Review Comments:

COMIRB noted the Chair review and subsequent deferral to full board performed on March 4, 2016. The Chair deferred this unanticipated problem report to the full board due to the need to assess if and how enrolling the subject in violation of inclusion/exclusion criteria impacted subject risk and to determine if the corrective action plan to prevent future occurrences of this type of event is adequate.

This unanticipated problem report submission and PI's written response to deferral has been reviewed by the committee and the following determination has been made:

NOTED

The committee reviewed the submitted UAP involving protocol deviation and determined that this protocol deviation did not present significant risks to subjects or others nor did it represent serious or continuing non-compliance.

Committee issues and concerns:

1. The committee noted that the study team followed up with the subject by obtaining consent over the phone and also, mailed the subject a consent form for the subject's signature. The committee agreed this plan was acceptable and recommended that the study team need not follow up with the subject again, if the consent form was not returned by the subject.
2. The committee determined that the subject's data can be used for safety and quality assurance purposes, but not to address the study end points because the study interventions stopped when it was discovered that the subject did not meet inclusion criteria so the data collected would not contribute to evaluating the study aims.

Other materials submitted:

1. Cover Letter dated March 4, 2016
2. Response submission Cover letter dated March 12, 2016

Other materials changes: None.

Please note that COMIRB will no longer be E-mailing approved documents. Stamped, approved documents can be retrieved in the eRA (InfoEd) system. [Please click here](#) to access instructions on finding these approved documents.

Sincerely,
UCD Panel A



Colorado Multiple Institutional Review Board, CB
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Aurora, Colorado 80045

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University of Colorado Hospital
Denver Health Medical Center
Veteran's Administration Medical Center
Children's Hospital Colorado
University of Colorado Denver
Colorado Prevention Center

Unanticipated Problem Deferred

24-Mar-2016

Investigator: Ernest Moore
Sponsor(s): Department of Defense~
Subject: COMIRB Protocol 12-1349 Unanticipated Problem
Review Date: 3/23/2016
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: UAP011-1

SUBMISSION DESCRIPTION:

Initial report of non-compliance/protocol deviation for enrollment of subject not meeting inclusion criteria for subject #C-096.

On 03/16/2016 at approximately 12:30, a trauma-activation was paged out with a 50's year-old male who sustained a gunshot wound with a pressure of 76/60 mmHg. No heart rate was provided on the activation page. The patient was enrolled into the COMBAT Study and was randomized to the experimental arm. The plasma transfusion was completed in the ED, and the patient was rapidly transported to the OR. The study PI, Dr. Moore, was present throughout the patient's entire ED course. Due to the nature of the injury and the chaotic emergency room situation, the study team was able to review the patient's Field vital signs and verify the inclusion criteria only after the plasma transfusion was completed and the patient departed the ED. During this review, it was discovered that, although the patient was hypotensive (76/50 mmHg) in the field, his heart rate was not high enough to qualify him for enrollment into the study (60 bpm). Neither blood nor any other study procedure was performed on this patient after inappropriate enrollment vital signs were recognized by our team.

The patient left the ED and went to the OR, after which he was transferred to the PACU and, subsequently, to the Correctional Care Medical Facility (CCMF) approximately four hours after his arrival to the hospital. On 3/17/2016, when

the patient was able to be consented, the study team attempted to consent him. However, the patient was discharged to jail just prior to a study team member informing the patient about his enrollment in the study. Our team attempted to contact the jail to set up a time to speak with the patient to discuss the study, however, all attempts have been unsuccessful (voicemail was left with call-back information). The patient has a follow up appointment at Denver Health on April, 12, 2016 at which point the study team will attempt to inform him about his enrollment.

As with any other type of blood product, there are certain risks associated with plasma transfusion (transfusion reaction, risk of infection, etc). The study team will discuss this with the patient to notify him about the enrollment and plasma transfusion.

Corrective Action Plan: No blood was drawn for research purposes after the study personnel became aware of the mistaken enrollment. The paramedic team was notified about the mistake and reminded about the selection criteria. This and other similar cases will be included in the paramedic refresher training in the near future.

Your COMIRB Unanticipated Problem submission UAP011-1 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. Please address the changes or clarifications as soon as possible.

[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: UAP011 reports enrollment of a subject not meeting inclusion criteria. Defer to full board for review.

No additional information is requested. UAP011-1 will be assigned to the next available Panel A agenda.

Sincerely,

UCD Panel A

Please provide Feedback on [Your Experience with the COMIRB Process](#)



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University of Colorado Hospital
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University of Colorado Denver
Colorado Prevention Center

Unanticipated Problem Deferred

24-Mar-2016

Investigator: Ernest Moore
Sponsor(s): Department of Defense~
Subject: COMIRB Protocol 12-1349 Unanticipated Problem
Review Date: 3/23/2016
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: UAP010-1

SUBMISSION DESCRIPTION:

Initial report of non-compliance/protocol deviation involving enrollment of a vulnerable population not approved by COMIRB for subject #C-097.

On 03/16/2016 at approximately 21:30, the COMBAT study staff was made aware of a code 10 trauma return of a male patient who sustained an anterior left-chest stab wound. Paramedics enrolled the patient into the COMBAT trial after assessing his vitals (BP 80/P, HR 112) and verifying eligibility for enrollment, at which point he was randomized to the study arm. Following arrival at Denver Health, the patient, who had not been forthcoming with any personal information in the ambulance, told the nurse his date of birth, which indicated he is 17 years old. The study team confirmed the patient's date of birth with the nurse and the accompanying police officer, and both verified he was under 18. Immediately following, the study team stopped the plasma transfusion (first unit) and did not begin transfusing the second unit because of the patient's age. No blood draws were performed upon discovering the subject's age. It is worth noting that this patient is large and mature in appearance. Based on the patient care report written by paramedics, it appears they believed him to be over 18 until after he arrived at the hospital and his date-of-birth was recognized.

The patient's mother, his proxy decision maker, was informed of the enrollment. The situation regarding the enrollment of a minor was explained, and she understood the circumstances and reasoning for the enrollment of the patient. An

information sheet outlining the study procedures was given to her. She had no questions or concerns at that time.

As with any other type of blood product, there are certain risks associated with plasma transfusion (transfusion reaction, risk of infection, etc). The study team discussed the risks with the patient's mother and provided an information sheet with additional information about the study. Blood draws were not performed on this performed on this patient after realizing his age.

Corrective Action Plan: Unfortunately, with severely injured patients, it is not uncommon to have crucial demographic data missing or incomplete. Often the patients are only properly identified after arrival to the hospital and after study interventions have begun.

Your COMIRB Unanticipated Problem submission UAP010-1 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. Please address the changes or clarifications as soon as possible.

[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: UAP010 describes the enrollment of a minor (vulnerable population not approved by COMIRB). Defer to full board for review.

****No additional response is requested. This UAP010-1 will be assigned to the next available Panel A agenda.****

Sincerely,

UCD Panel A

Please provide Feedback on [Your Experience with the COMIRB Process](#)

Dear Dr. Moore,

I attempted to contact you at 303-602-1820 and enter your last name. There were six individuals by the name of Moore, but your name is not a choice and I could not reach an operator.

I was calling to inform you that we have reviewed your protocol amendment, dated February 26, 2016, received March 17, 2016, requesting to include a minimal risk, noninvasive device in your study. This study protocol may proceed.

For future submissions:

1. Please do not lock down or certify the pdf document.
2. Please submit documents to CBER at the following address to avoid the delay in receipt.

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

Sincerely,

Sonday L. Kelly, MS, RAC, PMP

Regulatory Project Manager
U.S. Food & Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review
10903 New Hampshire Avenue
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Fax# 301.595.1128

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