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14. ABSTRACT

Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH) is a prospective, randomized, open-label, non-blinded trial to determine the effect of pre-hospital administration of thawed plasma (TP) on mortality, morbidity, transfusion requirements, coagulation, and inflammatory response in severely-injured bleeding trauma patients. Two hundred and ten eligible adult trauma patients will be randomized to receive either two units of plasma, to administered in-field , vs standard of care normal saline (NS). Main analyses will compare subjects allocated to TP to those allocated to NS on an intention-to-treat basis. Primary outcome measure is all cause 30 day mortality. Secondary outcome measures include coagulation and lipidomic / pro-inflammatory marker responses, volume of resuscitation fluids and blood products administered, and major hospital outcomes.
Demonstration of significant reductions in mortality and coagulopathic / inflammatory – related morbidities as a result of pre-hospital plasma administration would be of considerable clinical importance for the management of haemorrhagic shock in both civilian and military populations.

15. SUBJECT TERMS
Nothing Listed

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1. Introduction

- The subject protocol was approved by the Virginia Commonwealth University Institutional Review Board (IRB) on 8 September 2014. This protocol required approval of a waiver by the Secretary of the Army (SA) of the Title 10 United States Code Section 980 advance informed consent requirement; the SA signed the waiver on 12 February 2015. The protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army and USAMRMC human subjects protection requirements. Organization of study logistics and practice training in preparation for study start-up was completed and the study was opened for patient enrollment on April 1, 2015.

2. Keywords

- Bleeding, coagulopathy, inflammatory markers, massive haemorrhage, pre-hospital, shock, thawed plasma, TRALI, transfusion, trauma

3. Accomplishments

a. During this reporting period the VCU study protocol was converted from paper to an electronic version by M.J. Michael, RN and the following amendments to the general investigational plan were made:

- Correction of redundancy throughout the protocol, and the inclusion of descriptors to provide more detail about processes in the trial flow.
- Patient disclosure materials were updated to be in compliance with what we had written in our original IND about the risks associated with plasma transfusion. (Infection and Inflammation added, Other bleeding problems removed).
- Wording was changed to clarify what is deemed a reasonable time that the Study Coordinator begins the process of obtaining informed consent.
- Key personnel changes: Dr. Christopher Hogan, replaced Dr. Teresa Duane as the PUPTH study Co-PI and serves as the Trial Director in Dr. Spiess absence. Dr. Ronsard Daniel replaced Dr. John Clore as the Safety Monitor. Dr. Jeffrey Ferguson was added as a Co-PI and will act as EMS Liaison in the absence of Dr. Ornato.

These changes were submitted as amendments and received approval by the VCU IRB. Notification of these changes were reported to the FDA in the 2015 Annual Report and reported and approved by the USAMRMC ORP HRPO.
The PUPTH study is registered with Clinical trials.Gov and assigned Identifier NCT02303964.

b. The PUPTH study was audited by the VCU Clinical Research Compliance Officer and found acceptable.

c. The PUPTH Study opened for patient enrollment on April 1, 2015.

d. One patient is enrolled in the study.

e. A summary of the PUPTH Study protocol was completed providing a quick reference guide and documentation of compliance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6) , the Code of Federal Regulation on the Protection of Human Subjects (45 CFR Part 46) , and the NIDCR Clinical Terms of Award. The Protocol Summary is attached to this document as an appendix and all references made in section **e.** of the report title **accomplishments** are linked to the attached Protocol Summary.

1. The goals as stated for this reporting period were met. Safe and adequate delivery, storage, and handover of plasma from Blood bank to EMS and vice-versa were designed and implemented (Protocol Appendix H, p109.)

2. A seamless and error-free collection of blood samples from patients and delivery of samples to PUPTH personnel was designed and implemented (Protocol Appendix H, p111).

3. Completion and documentation of CITI, GCP, and Trial Protocol training for >100 EMS personnel was completed.

4. Blood sampling kits were created using a bar coding system that ensures all samples delivered to the coagulation lab are de-identified (Protocol Appendix H, p109).

5. A Seamless and error-free chain of communication between EMS and relevant parties (ED, Blood Bank) was designed and implemented (Protocol Appendix C, p95).

6. PRIORITY ITEM: Contact information channels were established for EMS providers for PUPTH protocol activation (Liaison with ED, MCV Communication/operations) Establish contact information channels for Biostatistics for PUPTH data collection, randomization (Liaison with ED, MCV Communications/operations) (Protocol, Appendix E, p106).

f. **Bio-Statistician / Data Management Report**: Edmund Glass, under the direction of Brian Bush, designed and implemented case report forms to support data collection for the study. Design was a multi-stage process, grounded in the work of our colleagues with the University of Colorado who are conducting the COMBAT study.

After initial consensus was reached, the data management team directed a study-coordinator walk-through for a sample patient, which -- as expected -- generated numerous additional revisions. We also coordinated with the VCU lab analyzing blood samples to streamline data acquisition. Where necessary, the electronic REDCap database was updated in tandem with paper-based forms to support timely data entry and generation of an analysis-ready dataset.

The team participated in numerous meetings, phone calls, and email exchanges to facilitate study logistics. Among others, we worked extensively with the VCU Transfer Center to design and test a straightforward intake process which administers randomization securely, documents the logistics of necessary medical approvals, and supports the paging of the study team at enrollment. We worked with the study coordinator team to enhance this process after mock trials with both participating EMS providers (Henrico Fire and Richmond Ambulance Authority).

We communicated with a sister study (University of Pittsburgh) regarding data harmonization. We participated in meetings with TACTIC (Trans-Agency Consortium for Trauma-Induced Coagulopathy) personnel.

Dr. Wegelin contributed to the following article which was submitted to Trials and accepted for publication (after revisions): Penny S Reynolds, Mary-Jane Michael, Emily D Cochran, Jacob A. Wegelin, and Bruce D. Spiess, Prehospital Use of Plasma in Traumatic Hemorrhage (The PUPTH Trial): Study protocol for a randomized controlled trial.

After the "go live" date, when only one study participant was enrolled in the study for several weeks, we took the initiative to plan for a self-audit to investigate what was causing this dearth.

We also provided miscellaneous technical guidance to the team in support of study-related activities, including configuring generic email accounts and serving as a telecommunications liaison by fielding inquiries related to call forwarding and paging groups.

f. **Transfusion Medicine Report**:

Completed by: Steven Armstrong, MSHA, MT(AMT), SBB(ASCP), FACHE
Manager, Transfusion Medicine
VCU Medical Center

Scope of Work: The transfusion medicine department is responsible for the following PUPTH study items within FDA, AABB, and CAP guidelines:

- Ordering and Maintenance of Adequate Plasma Levels
- Storage of Frozen and Thawed Plasma
- Thawing of Plasma
- Labeling of Plasma
- Tracking Plasma
- Inventory Management of Issued Plasma
- PUPTH Study Portable Storage Devices
    - Selection of storage devices
    - Use of storage devices
    - Validation of storage devices
    - Maintenance and cleaning of storage devices
- PUPTH study electronic temperature monitoring devices (eTMD)
    - Selection of eTMD

    - Use of eTMD
    - Validation of eTMD
    - Storage of eTMD
    - Maintenance of and cleaning of eTMD
    - Data recovery
    - Data storage
    - Data maintenance
- PUPTH study temperature indicator devices (TID)
    - Selection of TID
    - Use of TID
    - Validation of TID
    - Storage of TID
    - Inventory management of TID
    - Data maintenance
- Training of Emergency Response Personnel
    - PowerPoint development
        - Transfusion practices
        - Adverse event recognition
        - Initial competency assessment
        - Annual competency assessment
    - Training and Instruction
        - RAA
        - Henrico
- Training of Transfusion Medicine Staff
- Procedure Development
    - Assigning, Issuing, and Returning PUPTH Study Plasma
    - PUPTH Study Quality Control
    - PUPTH Study Personnel Training and Competency
    - Deviations from PUPTH Study Protocol
- Procedure Validation
- Form Development
- Anti-B Titer Protocol and Testing
- IND and IRB Submission Information and Document Review
- Communication and Follow-up
- Issue Resolution and Follow-up

Working Timeline: All of the PUPTH study transfusion medicine department's work effort was completed prior to the start date of the study (April 2015). Since the beginning of the study, transfusion medicine has been actively involved in supporting the study and ensuring all plasma units are stored and utilized per study protocols and applicable regulatory requirements.
Prior to the end of the 2015 calendar year, competency testing of all involved personnel will be conducted.

4. IMPACT

- Nothing to report

5. CHANGES / PROBLEMS

Patient enrollment began on April 1, 2015. 1 patient enrolled in study. We are addressing our patient enrollment numbers and are currently working with the trauma registry to review and evaluate trauma admissions that we identify as "screen failures" (Meeting criteria but failure to

enroll). Meetings are scheduled with each of the QA directors at the 2 EMS agencies participating in the study to review and compare trauma call sheets to the trauma registry. A meeting was held with the director of Med-flight Services to evaluate potential use of helicopters in addition to EMS vehicles. The feasibility of expansion to a larger catchment area with regards to available resources will be made.

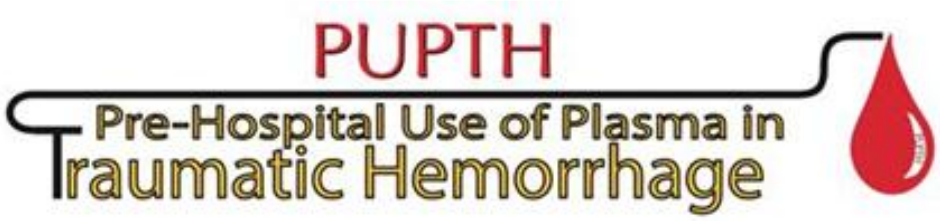
6. PRODUCTS

The PUPTH protocol was accepted for publication in the journal TRIALS. (attached)
Reynolds PS, Michael MJ, Cochran ED, Wegelin JA, Spiess BD. Prehospital Use of Plasma in Traumatic Hemorrhage (The PUPTH Trial): Study protocol for a randomised controlled trial. *Trials*, **(in press)**
(Attached as PDF in Appendices)

7. Appendices:

1. Version 2 PUPTH Protocol SOP
2. Accepted Protocol for publication

Pre-Hospital Use of Plasma in Traumatic Hemorrhage



VCU IRB Protocol Number: HM14813
Grant Number: W81XWH-12-2-0022

Principal Investigator: Dr. Bruce Spiess, MD, FAHA

Medical Monitor: Dr. Ronsard Daniel, MD

Draft or Version Number: 2.0

June 25, 2015

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Bruce D. Spiess, MD, FAHA

Title: Principal Investigator

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LIST OF ABBREVIATIONS

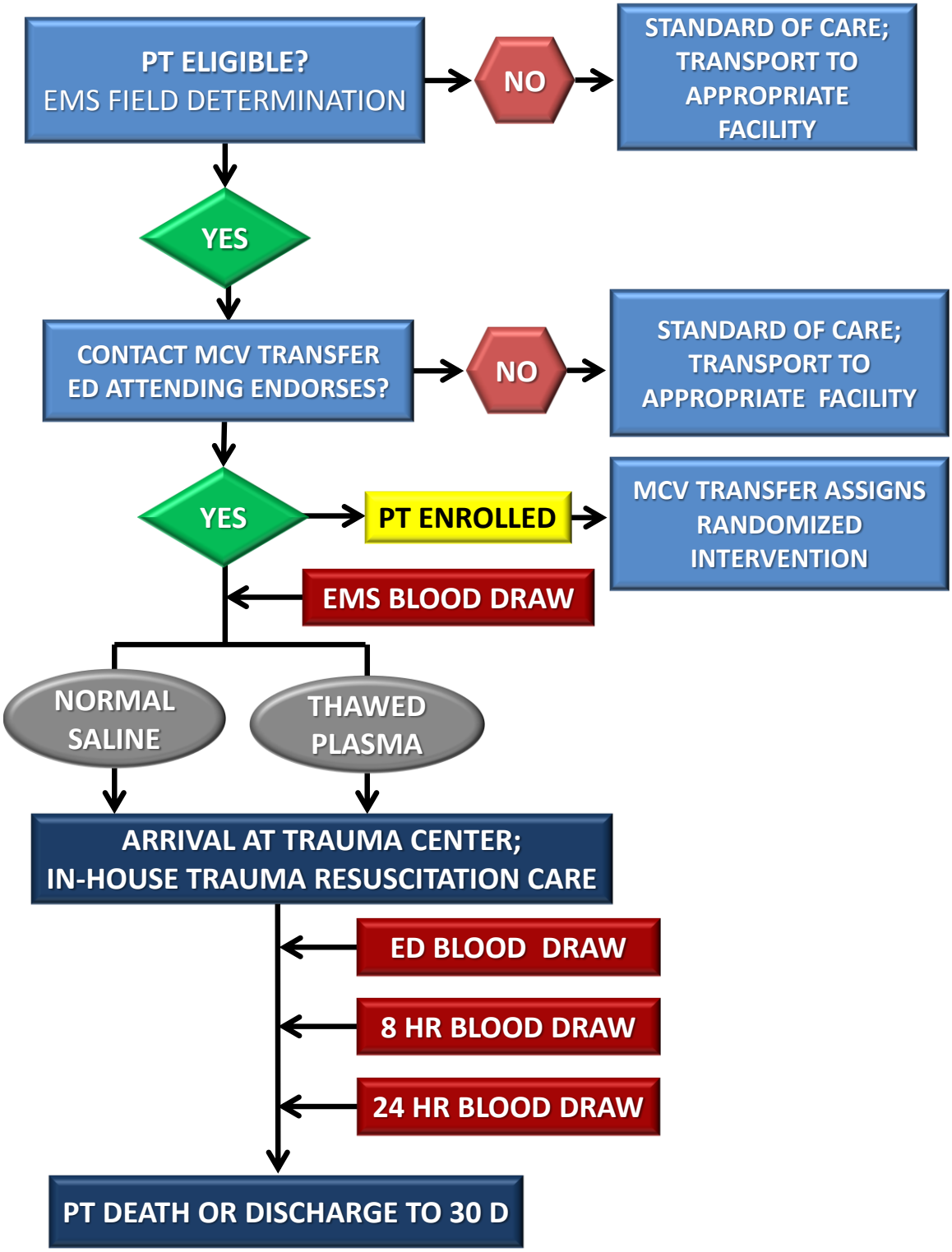
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSOC	Clinical Study Oversight Committee
DHHS	Department of Health and Human Services
DMFS	Decayed, missing, and filled tooth surfaces
DSMB	Data and Safety Monitoring Board
EMS	Emergency Medical Services
eCRF/CRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LAR	Legally Authorized Representative
MH	Major Hemorrhage
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PTr	Post-trauma

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TP	Thawed Plasma
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

Title:	Pre-Hospital Use of Plasma for Traumatic Hemorrhage – (PUPTH Study)
Précis:	In this study, eligible patients with polytrauma (PTr) and major hemorrhage (MH) will be given either standard normal saline or TP in the pre-hospital setting.
Objectives:	The primary objective of this study is to compare the 30-day mortality between patients receiving NS and TP in the pre-hospital setting.
Phase:	Plasma: Phase II Normal Saline: Phase III
Number of Sites:	This is a single-site study.
Study Duration:	36 months from enrollment to analysis.

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

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Institutions:	Virginia Commonwealth University 1201 E. Marshall St. Richmond, VA 223298
Other Key Personnel:	Mary Jane Michael, RN Lead Study Coordinator VCU Department of Anesthesiology 628-3247 (office) 4507 (pager) mmichael@vcu.edu

2 INTRODUCTION

2.1 Background and Rationale

hemorrhage (MH) continues to be the leading cause of death for poly (multiple) trauma (PTr) patients in both civilian and military medicine.[1-5] In armed conflict, traumatic amputation and major truncal injury lead to the potential for massive and poorly controlled major hemorrhage (MH).[1-5] Early, first responder, pre-hospital utilization of tourniquets, new coagulant stimulating bandages, permissive hypotension (partial resuscitation and other factors) are contemporary efforts to reduce MH, yet 80% of the mortalities associated with military combat happen in the field 55-60% occur in civilian PTr).[5-8,12] Overall, PTr carries a 40-50% mortality.[5,13] Deaths from PTr can be categorized into those that occur immediately due to uncontrolled MH and those that are associated with multiple organs that fail due to complex and interrelated series of events. Both ICU or secondary in-hospital deaths and multi system organ failure (MSOF) are potentially impacted by early/overall reduction of hemorrhagic shock as well as total blood

Table 1: Sequential Organ Failure Assessment (SOFA) Score to be used to define MSOF.[99]

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	< 400	< 300	< 200	< 100
			with respiratory support	
Coagulation Platelets $\times 10^3/mm^3$	< 150	< 100	< 50	< 20
Liver Bilirubin, mg/dl (μmol/l)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	> 12.0 (< 204)
Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Score	13 – 14	10 – 12	6 – 9	< 6
Renal Creatinine, mg/dl (μmol/l) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440) or < 500 ml/day	> 5.0 (> 440) or < 200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

The SOFA score can be used to predict outcomes and mortality in ICU patients and is calculated with the worst values on the day observed.[99, 100] This research could impact

PTr/MH leads to a complex coagulopathy.[14-19] early hypotension and shock and late MSOF complications of PTr are, attributable to blood loss and tissue destruction combined with the side

effects of therapy (fluid infusions and transfusion etc.). Release of tissue factor, collagen, von Willebrand factor and phospholipids contribute to the complexity of the coagulopathy. The protein cascades, platelets and immune systems are all activated to some degree.[14-20] MH leads to loss of protein/platelet coagulation precursors. Shock precipitates further activation of inflammatory/coagulation cascades. Each system has cross talk and feedback loops which regulate further reactions (Figure 1). Traumatic brain injury (TBI) leads to profound release of phospholipid and large, activation of plasminogen fibrinolytic pathways.[21, 22]

Transfusions are pro-inflammatory, carry cytokine loads, reduce critical oxygen delivery through the microcirculation, and transfer cell micro-particles (an inflammatory inciting event and one characterized by lipids.[23-30] A large and persuasive gathering of literature is showing that patients transfused have much worse outcomes.[23-30] Cause and effect are as yet not fully proven, but in the few existing randomized studies, transfusion never out performed not transfusing.[31] Ethically, no randomized trial can be done of transfusion in PTr/MH. Transfusion in PTr/MH is widely accepted as lifesaving particularly with fresh whole blood. That being said, in the trauma literature, the conclusion that levels of transfusions are associated with more death, increased length of hospital stay, more MSOF and other adverse events is supported.[32-42] There is evidence to support that massively transfused patients have more renal failure (dialysis dependent), lung dysfunction, infections and MSOF than do those patients receiving less transfusions. What cannot be sorted out from the mounting literature are the effects of survivor bias and evidence that those with a greater Injury Severity Score (ISS) require more blood transfusions. Importantly for this study, current research shows that patients receiving greater than 6 units of fresh frozen plasma who do not demonstrate a clear coagulopathy have shown worse lung function than those receiving less plasma.[38] The reduction in transfusion is not a simple subject; however any therapeutic early intervention aimed at decreasing total transfusion load should, in theory, improve patient outcome. The key may well be to decrease hypotension, shock and endothelial cell hypoxia, catecholamine driven perturbations.

Coagulation historically has been thought to be a protein process. Contemporary understandings of bleeding/thrombosis homeostasis find that the process is largely a cell based interaction between circulating serine protease cascades that are both activated and inhibited, the binding of these proteins to expressed platelet binding sites, and the interaction with normal or perturbed endothelial cells.[43-47] A resulting highly localized vascular wave (Figure 2) of initiation, activation, control and recanalization takes place.[47,48] If localized control mechanisms are overcome or the entire body cycles out of control, then systemic diffuse coagulopathy results (diffuse intravascular coagulation- DIC, consumptive coagulopathy).

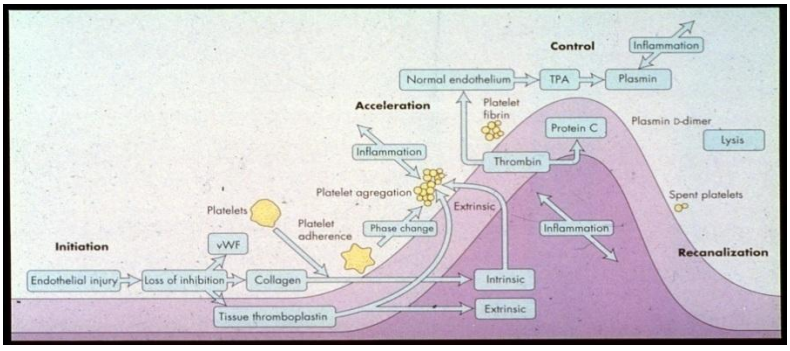


Figure 2: The localized flow of coagulation is a wave of highly controlled cellular and protein activity starting with an initiation phase going on to acceleration, control and re-canalization.

Platelets are highly dynamic cells that can undergo partial or total activation.[15, 49-51] If only partially activated platelets can revert to a quiescent state. Once completely activated granules expelled, platelets are spent and cannot participate in thrombotic/coagulation functions. Platelets once initially activated quickly can convert to being dysfunctional. The protein release by PTr/MH leads to expression of adhesion ligands (GPIb-IX complex) and eventually fibrinogen adhesion (GPIIb-IIIa) as well as granular release (CD-62). The inflammatory cytokines can activate as well as inhibit platelet functions. Disseminated intravascular coagulopathy (DIC) products can inhibit serine protease binding to key cell ligands and thereby promote bleeding themselves. Bleeding begets bleeding, inflammation feeds back resulting in up regulating and worsening inflammation. Once activated, the platelets provide complex feedback loops to multiple serine protease inputs in both the coagulation and inflammatory cascades. These feedback loops serve to amplify and feedback (Figure 22). In the end a very complex, unpredictable consumptive coagulopathy is possible. The severity of the coagulopathy of PTr/MH in trauma has repeatedly been shown to be a predictor for morbidity and MSOF. Table2 shows protein markers increased and decreased in trauma. The relative amount of increase/decrease of each of these markers is highly variable patient to patient.

Coagulation Markers	
Increased	Decreased
Procoagulant activity/tissue factor	Platelets
Fibrinogen	Antithrombin III
Thrombin-antithrombin	Protein C antigen
Fibrinopeptide A	Protein C inhibitor
Prothrombin fragment 1 + 2	Protein S
Plasmin α_2-antiplasmin complexes	Factor VII
D-dimers	Factor XII
Thrombomodulin	
tPA activity	
tPA antigen	
Plasminogen activator inhibitor-1	
von Willebrand factor	
von Willebrand factor propeptide	
Platelet thrombospondin	

tPA, tissue plasminogen activator.

Table 2: Coagulation proteins/proteases, and platelets that either increase or decrease as a result of PTr. A number of these levels could be affected by the early use of TP.

Early arrest of bleeding and early restoration of perfusion pressure/vital signs are important to survival in PTr/MH.[52-54] Circulating blood volume, oxygen delivery, red cell mass, and coagulation factor restoration are all important parts of PTr/MH resuscitation. Fresh whole blood is the “gold standard” by which all other resuscitation fluids should be measured.[55-57] Fresh whole blood cannot be compared to man-made pharmaceutical IV infusion fluids. Currently there is no available replacement for fresh whole blood nor is ta “best” resuscitation fluid for PTr/MH. A recent symposium on the subject held by the US Army Institute of Surgical Research (ISR) and the Combat Casualty Care Research, US Army Medical Research and Materiel Command carefully reviewed the status of available intravenous volume replacements. The last such review was approximately 10 years prior.[58] Present Tactical Combat Casualty Care (TCCC) recommendations for PTr/MH patients

in shock are to receive 6% hetastarch with calcium (Hextend, Baxter Inc., Deerfield, IL.) as a 500 ml rapid infusion.[5] Other options have included normal saline (NS), Lactated Ringers (LR) solution, and hypertonic saline (HS). The literature is extensive comparing various combinations of these solutions under different conditions in both civilian PTr/MH and combat casualty PTr/MH. Hextend (a model colloid) preferred by the military remains intravascular once infused and has at least an 8 hour half-life. Hextend recruits other extra-vascular fluids as compared to crystalloids[5] that leak from normal vascular structures such that, at least 3 times as much fluid must be IV infused as will be found circulating 10 minutes after resuscitation. To create an equal amount of central (heart filling) circulating volume increase, the crystalloids need far more volume. In battle the cube weight of fluid solutions carried by a combat medic is of logistical importance, hence the TCCC calls for the less weight of Hextend.[5] Notwithstanding the TCCC recommendations,50% of PTr/MH combat injuries do receive NS as the first fluid.[5] Normal saline is often recommended as the first line fluid for civilian PTr/MH resuscitation. The support for that however is of great controversy.

Hextend, a starch product even with calcium added, likely contributes to a diffuse platelet dysfunction and von Willebrand factor (factor VIII) reduction leading to coagulopathy.[59, 60, 61] NS contributes to hyperchloremic metabolic acidosis.[62] Lactated Ringers (LR) is more acidotic than NS and advised not to be utilized with banked blood products. Lactated Ringers contains calcium and adds to intravascular lactate and has both racemic (dextro- [known as D-]and levo- [known as L-] rotatory forms of a molecule) isomers of lactate.[63] The D-isomer cannot be metabolized by humans to bicarbonate therefore the commercially utilized LR, increases pro-inflammatory neutrophil activation.[63] Plasmalyte (PL), another crystalloid, has the disadvantage of containing magnesium which can lead to worsening shock.[64] Five percent and 25% albumin are effective colloid solutions that, although theoretically can transmit human viruses, have not done so since 1987.[65] These preparations are far more expensive than either Hextend or crystalloids and can only be transported in glass bottles (not battlefield compatible). Post-resuscitation, albumins are associated with increased levels of respiratory dysfunction and can affect coagulopathy by decreasing fibrinogen. Three percent and 5% saline and 7.5% hypertonic saline are under investigation compared to each of the other crystalloid and colloids, especially in the face of traumatic brain injury (TBI).[66] In summary, no existing colloid or crystalloid has been shown to universally or convincingly stand out. Crystalloids tend to increase extra-vascular fluid, abdominal compartment syndrome, increase inflammation and lead to acidosis. The colloids, expensive products, have problems with being retained in the extra-vascular space as well as coagulopathy. Other than intravascular volume increase, neither colloids nor crystalloids supply any fundamental functions of fresh whole blood.

Plasma/ Reduced Mortality: Historically, plasma was utilized in the early days of blood banking and combat for trauma resuscitation.[5, 67] In WWII both liquid plasma and freeze dried plasma were used. Currently a German Red Cross freeze dried (lyophilized) plasma product is in use in Thailand and South Africa.[67] In the 1960's, blood banks established universal component separation. At that point, blood banking fundamentally changed because whole blood, freeze dried plasma and FFP were no longer available forward in combat. In civilian medicine whole blood is currently unavailable, except in very rare circumstances.

Today, the mantra of blood banking is that three or more lives can be saved from a single volunteer donation. During recent military conflicts, massive transfusion protocols (MTP) with

1:1:1 use of red cells to FFP and platelets have shown success.[18,19,68-74] Similar work was done in civilian PTr/MH demonstrating improved outcomes. Massive transfusion protocols are "work-arounds" for not having fresh whole blood available. There is increasing support that early institution of coagulation therapy improves outcome and limits overall use of blood products when large blood loss has occurred. The transfusion fluids delivered when the MTP is implemented are like that of reconstituted and stored form of whole blood. Such therapy carries the risks of multiple donor exposures and the effects of storage lesions. Early intervention with warm fresh whole blood (WFWB) decreased mortality 37% in treatment of combat PTr.[57] However; WFWB is not available without cross-matching.

Early intervention with repletion of lost plasma proteins may be of use in PTr/MH. A swine model of uncontrolled hemorrhage shows that early intervention with plasma was superior to all other interventions.[75] That research result parallels prior combat experiences suggesting that forward movement of blood products, particularly coagulation precursors/TP convey benefit in PTr /MH. Indeed this recent animal-based research represents a movement "back (WWII) to the future".[75] Our Virginia Commonwealth University Reanimation Engineering Science Center (VCURES) research group just completed animal studies of spray dried plasma and platelet products in an Office of Naval Research (ONR) sponsored series of studies. These studies represent pre-clinical development proof of efficacy studies in PTr/MH.

An emerging literature exists to demonstrate that early utilization of TP may decrease mortality in PTr/MH. Beginning February 2010 at the University of Texas Health Science Center, Houston, Texas Emergency Department (ED), TP was stocked in the ED to allow for the rapid availability of TP for trauma patients. A retrospective analysis of the 8 months prior to the institution of stocking TP in the ER and 8 months after its commencement showed that in 294 patients (130 prior to the TP first usage, v. 164 after institution of the new policy) trauma patients received TP 46 minutes earlier than those who had to wait for plasma to be delivered from the blood bank. Those who received TP early had an overall reduction in transfusion of both packed red blood cells (RBCs) and other plasma products but demonstrated the greatest reduction in platelet transfusions. Logistic regression noted that the early use of TP was an independent reducer of 30 day mortality (odds ratio, 0.43; 95% CI, 0.185-0.956 P=0.04). [76] This group has now moved plasma out to their helicopter rescue services.

In a larger cooperative, prospective, multi-centered study of trauma victims, the PROMMTT study, higher ratios of plasma and platelet utilization and early intervention with plasma had an independent association with decreased 6 hour mortality, yet at 24 hours (survivors at this time) the 30 day mortality was not influenced by the ratio of plasma usage.[77] A total of 1245 patients from ten level one trauma centers were enrolled in this study; however, the study design did not have constant and controlled ratios of plasma nor did it answer the question that we wish to answer in the PUPTH study. Indeed the PROMMTT study did not prospectively task emergency response teams to administer plasma first. The severity of bleeding and the total amount of all blood products administered were associated with worsening mortality. [78, 79] There was no increased hypoxia related to the extensive and early use of plasma. Severity of injury and thoracic injury appeared to overshadow any risk factors from Transfusion Related Acute Lung Injury (TRALI) associated with a liberal and early use of TP. [80]

Another retrospective study of massive transfusion protocol utilization in which early and large amounts of plasma were utilized was performed at the University of California, San Francisco. Of 437 transfused patients, the coagulopathy of trauma was an independent predictor of mortality. As the ratio of TP to pRBCs increased, mortality was decreased. [81] A meta-analysis was recently performed looking at 20 studies of massive transfusion protocols.[82] Together these studies contained a total of 12,154 patients receiving varying ratios of plasma to pRBC's. Fourteen of the 20 studies reported lower 30 day mortality associated with high administration of plasma to pRBC ratios, whereas six studies noted no discernable difference. No studies demonstrated a worsened outcome when using high plasma to pRBC ratio.[82]

In conclusion there is substantial evidence that high ratios of TP utilized early in treatment of PTr/MH reduces mortality, may improve TIC and may decrease overall transfusion utilization. There are questions of survival bias in these retrospective analyses of data bases, and of course the studies quoted above do not look at pre-hospital usage of TP. [83]

Plasma Group/Composition Rationale: The blood banking industry separates blood into components. Plasma is separated from whole blood by differential centrifugation. If it is frozen (to -18 C or colder) within 8 hours of collection (6 hours if prepared with Acid-Citrate Dextrose), it is called "fresh frozen plasma" (FFP). Within a unit of FFP (approximately 225 ml) the concentration of plasma proteins is similar to fresh plasma (slight reduction of factors V and VIII). If the plasma is frozen within 24 hours of collection, it is referred to as "plasma frozen within 24 hours" (FP24). Though the exact concentration of the labile factors (V and VIII) differs slightly, these products are thought of as functionally equivalent. Once the FFP or FP24 is thawed, it can be held at 4 C (FDA accepted range 1-6 C) for up to 24 hours and is referred to as either "thawed FFP" or "thawed FP24". After 24 hours at 4 C, the product must be renamed "thawed plasma" and may be stored for an additional 4 days (5 days total, from time of thaw).

Plasma may be given as either type specific or universal donor. Group AB plasma should be thought of as the universal donor plasma. However AB blood type accounts for only 4% of the North American population. [84-86] There are very limited supplies of group AB plasma. If we were to use it for our study alone, an undue burden would be placed upon the blood banking community of Central Virginia. Furthermore, if the PUPTH study is successful and a generalized pre-hospital use of TP is put forward across the country for PTr patients, the future supply of AB plasma would be impossible to meet the demand. There is limited reason to do a research study for which, if it is successful, there is no way for it to be generalized to all of medicine.

We have chosen to utilize group A plasma as a next best option. Other centers have previously looked at the use of group A plasma in trauma. [87-90] At the Mayo Clinic in Rochester, Minnesota a research team studied the use of "in flight" blood resources. Through work from their blood bank the rotary winged aircraft carries 2 units of thawed plasma A + and A- and 4 units of O- packed RBCs on each flight. The emergency flight team have a massive transfusion protocol that is invoked based upon the same hypotension, tachycardia and bleeding criteria that are established for the PUPTH study. Recently the Mayo Clinic Institutional Review Board approved their retrospective analysis of data comparing 9 patients who received plasma compared to 50 patients in the control (historical only) group. [87] Those patients involved in the "in flight" blood administration program had plasma initiated 131 minutes sooner when compared to those not in the program. Those who were involved in the study came closer to a 1:1 ratio of TP to pRBCs than those who received blood

products on entry to the hospital. This was not a matched study and the patients receiving TP had a much higher injury severity score as well as a predicted mortality. Acute respiratory disorder syndrome (ARDS), acute renal failure (ARF), hospital stay and ICU length of stay were not different in survivors, but mortality (as predicted by the injury severity score) was higher in the group that received plasma. The group from Mayo concluded that the use of A plasma was feasible and noted no evidence of acute reactions to the A plasma. However, the study demonstrates the need for a larger study (as the PUPTH one) to examine efficacy of the plasma in matched (randomized) groups of patients.

Maintenance and use of thawed A plasma within the ED has been written about by the Mayo Clinic (prior to their use on rotary winged aircraft) and by Dartmouth Medical Center. [88, 89] Both centers recognized the impracticality and strain caused by maintenance of AB plasma and its potential wastage as a scarce resource. They noted that there would be some risk of anti-B antibody and at least the potential for intravascular hemolysis as reported with out of group platelet transfusions.[90-95] These groups note that comparisons when made were to type O cross reactivity to type B recipients (about 13% of the population). It was noted that group O donors carry a higher titer of anti-B than group A donors (platelet concentrates). To date, there has only been one case report in the literature of a group A platelet transfusion to a group B patient resulting in hemolysis, and it was later confirmed that this donor had high titers of anti-B.[95] It was thought to be that the high titers in this particular donor were due to use of pro-biotics. [95] We will use pre-screened low titer (<1:100) plasma to further reduce the chances of any reaction. The group from Dartmouth looked at all of their A plasma and found 2 units out of 98 screened to have titers above that level. Neither Mayo clinic nor Dartmouth has seen any evidence of hemolysis in their trauma patients who received A plasma for early resuscitation.

Plasma has been implicated as a source of inflammatory mediators that can lead to Transfusion Related Acute Lung Injury (TRALI). [96, 97, 98] [98]TRALI is the most common cause of transfusion related mortality. [96, 97, 98] Uncross-matched plasma has been associated with increased adverse outcomes, but these data are not always in the context of limited use (2 units) for acute PTr/MH.[79] The events of MH, shock, traumatic brain injury and/or bone fracture can alone or in combination cause lung dysfunction, so it is near impossible to sort out any causally related events due to blood usage in the face of PTr/MH. At the present time, the standard of care for patients presenting to combat care sites or civilian ED facilities is early and rapid administration of intravenous plasma without full cross match. As soon as cross match is available, and if matching units can be found, these matched products are used.

Logistically, the deployment of pre-hospital blood products is challenging Storage of and control over blood products is carefully controlled by the United States Food and Drug Administration (FDA) regulations and American Association of Blood Banks (AABB) guidelines. Because of the time it takes to thaw (22 minutes or more) and the logistics of thawing in the field, FFP is not a viable option for our center in this study; previously; P thawed plasma products that can be placed in an approved, validated refrigerator in an emergency medical service (EMS) vehicle represent a better option for our EMS groups. A challenge is to keep 4 4° C (range 1-6° C) stored plasma readily available for use in the first responder vehicle as well as the ED... Necessary steps include validating technology for in-field storage of thawed plasma, creating a schedule to rotate

supplies, training personnel in proper storage and administration of plasma, and developing standard operating procedures for the evaluation of returned, unused plasma to the blood bank.

To date no large scale human testing of TP versus normal saline has been undertaken prior to hospital entry. The PROMMTT study previously discussed began intervention within the hospital ED. Historical reports of good outcomes using plasma in WWII, notwithstanding, this proposal therefore stands as a "first in humans" randomized human trial. Such "first in human" trials related to pharmaceuticals are focused upon safety. In this case, the product in question, TP, is already standard of care in PTr/MH which makes this trial distinctly different than such pharmaceutical trials. Safety remains paramount and plasma products have demonstrated that safety in PTr/MH in the hospital. The trauma literature does show that early intervention with plasma has enhanced survival benefit. In our region (greater Richmond area), the transport time from site of injury to ED is 6-20 minutes. This study takes an existing highly recommended/tested therapy (TP for PTr/MH) and moves it forward in timing (to the site of injury). Nothing will change in terms of the proven composition or safety of the blood product to be infused (TP) in this human trial.

In summary, the background shows that plasma improves survival, decreases overall coagulopathy after PTr/MH and is already the standard of care upon arrival in the ED. Laboratory/animal testing supports improved outcome by moving the usage TP forward in timing, where historically plasma has been used. The human trial of TP is called for in the recent Pre-hospital fluid conference sponsored by US Army ISR- Materiel Command and TCCC.

Public Purpose: PTr is the leading cause of mortality for individuals under age 45 in the civilian population. When considering productive years of life lost (including but not limited to taxpaying dollars, head of household, long term disability payments) major trauma in the civilian population is far more costly than those chronic conditions most often the result of aging such as heart disease, stroke and cancer combined. Major trauma receives far less funding from the National Institutes of Health (NIH) than do the other diseases mentioned. If this trial shows efficacy in reducing mortality, length of stay, ICU stay, ventilator days, infection, and MSOF from the early forward use of thawed plasma, this will be a significant advance for the civilian population. Subsequent research studies will then be warranted to examine how much cost/benefit there is in generalizing the forward deployment of plasma to EMT/EMS first responders for the civilian population.

Blood products/transfusion are a mainstay of modern medicine. Fourteen to 16 million units of blood are collected/utilized per year in the United States. Allogeneic blood is therefore a dear/precious resource. Trauma accounts for approximately 8-12% of blood usage in the US. If moving plasma forward in the treatment paradigm results in significant savings in blood demand, that would have far-reaching positive benefits for US civilian healthcare. Allogeneic stored blood is a homeland security commodity. In Israel and Great Britain, stockpiles of blood are kept for conflict driven large casualty loads. In the US, 1.3-1.5 days of available blood supply are on hand. Therefore, any effort to decrease demand increases stockpiles and is, in itself, a homeland security/disaster preparedness commodity. We have commented upon our rationale for the use of group A plasma and feel it is of best public benefit to use this rather than group AB. If this study proved successful utilizing group AB, the generalization of the pre-hospital use of plasma would potentially create a shortage of AB plasma.

In In addition, improvements in survival and increased functional level of veterans who in the future get early plasma intervention could impact rehabilitation and movement from VA dependent

chronic disability status to employment. That change in status, even if for a small segment of the military population, could have an impact upon the civilian world.

2.3 Potential Risks

Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. The risks associated with the forward infusion of a maximum of 2 units of TP (see risk and risk reduction pages XX – XX) are judged to be reasonable compared to the risk of death in these patients. In addition, the current standard pre-hospital fluid therapy normal saline, carries it's own risks, as it contributes to hyperchloremic metabolic acidosis which makes organ function worse and leads to dysfunction of coagulation proteins and worsening platelet function. Also, TP is given to patients as standard of therapy once the patient reaches the Emergency Department (ED). The use of group A, low anti-B titer TP has been explained above and is the standard at a number of key Level 1 major trauma centers in the United States. The risks of group A plasma, although not zero, are less than the benefit expected from early resuscitation with 2 units of TP for patients of PTr/MH.

1.The diseases and adverse effects of the plasma TP are the same as those of all allogeneic (donor different from recipient) blood products including

- Potential transmission of viral and other parasitic infections. The risk of contracting hepatitis B from transfusion is estimated to be 1:280,000 to 1:357,000, while the risk of contracting hepatitis C and HIV is much smaller (roughly 1:1.1million to 1:1.7 million for hepatitis C and 1:1.4million to 1:2million for HIV) due to the implementation of nucleic acid testing.[1,2] The exact risk of contracting a parasitic infection such as trypanasoma cruzi (Chagas disease) from transfusion is unknown, since these cases are so rare.[3] Look-back procedures will be followed if it becomes necessary to alert a patient that they were transfused with a product from a donor who subsequently showed signs of infection (see Lookbacks/recalls IND Appendix 6).
- A risk of allergic reaction (including rarely from IgA deficiency) is possible. The occurrence of an anaphylactic allergic reaction (hypotension, bronchospasm/respiratory distress, urticaria) is estimated to be 1 /20,000 to 1/50,000, while urticarial reactions (urticaria, pruritus, flushing) occur in approximately 1/33 to 1/100 transfusions. The EMS personnel will be trained to recognize and react to such allergic reactions. Transfusion Related Acute Lung Injury (TRALI) is the most common risk of any blood transfusion, may occur as frequently as 1/5000 units of plasma transfused. TRALI is characterized by hypoxemia, respiratory distress, fever, bilateral pulmonary edema and hypotension. The EMS personnel will be trained to recognize and react to such allergic reactions.
- The use of group A TP (rather than universal donor group AB) presents a risk of hemolysis in patients with B antigen on the surface of their red blood cells (group B and group AB). In order to minimize this risk, the blood bank will perform titers for anti-B in al TP to be used in this study. Only those TP units with anti-B titers less than 1:100 will be dispatched to the EMS supervisors for this study (see IND Appendix 6 for tittering procedure). The EMS personnel will be taught how to recognize the possible signs and symptoms of a hemolytic reaction and what to do if such a reaction is suspected. The risks described above are the same risks encountered by trauma patients receiving TP

in the emergency department of VCUMC. The risk of these adverse events does not change depending on where the product is given. Just because polytrauma patients receive the TP in the pre-hospital setting does not necessarily mean they will receive more total TP. In fact, if the TP is successful in improving the patient's coagulation state, the study patients may be transfused with the same amount or fewer total blood products than those treated with normal saline.

2. Since the TP to be infused is stored at 1-6 C and will not be warmed prior to being given to the subject, there is a possibility of short-term hypothermia (lower than normal body temperature). This effect, if experienced, is likely to be transient and it is not anticipated that the patient will experience any untoward effects because of their slightly low body temperature.

3. Those in this study will be subject to additional venipunctures or arterial stick for research laboratory studies. There will be a total of 80 mL blood drawn over 4 time periods. Each draw will fill 4 tubes each with approximately 5 mL; total per draw is 20 mL. This will be repeated each time period (prior to study infusion by EMS, at 30 minutes post ED arrival, 8 and 24 hours). The blood loss due to these laboratory studies is small compared to the overall patient blood volume. The additional blood draws may cause some discomfort and bruising at the venipuncture site and a slight risk of infection, but no more than that caused by routine hospital blood draws. The EMS and hospital personnel drawing blood from the patient will use proper technique in order to minimize the discomfort and infection risk involved with venipuncture/arterial sticks.

3. It is possible that individuals with religious (e.g. Jehovah's Witnesses) or other objections to receiving blood products might become enrolled in the study if they are not wearing the opt-out wrist band, lack available documentation for EMS or do not have a family member at the scene to alert EMS about the patient's preferences. The EMS personnel are accustomed to looking in wallets for identification, and Jehovah's Witnesses have a standard issued card that they carry noting their objection to receiving blood products. It will be part of the training for the EMS supervisors that the importance of searching for such a "do not transfuse" card and documenting that this search was performed will be emphasized.

2.4 Potential Benefits

Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;
Patients in hemorrhagic shock from traumatic injuries are in a life-threatening situation and require early resuscitation by EMS personnel.

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
As described in the background section (IND pages 22-24), preclinical studies as well as clinical studies involving early use of TP in the ED and rotary wing aircraft have demonstrated the importance of early plasma administration. Based on this information, it is anticipated that the patients enrolled in this study who receive TP will have improved survival.

- Participation in the trial may improve mortality (decreased risk of death) for those receiving TP.
- Participation in the trial may reduce the chance of organ failure for those receiving TP.

Participation in the trial will aid in early recognition of trauma induced coagulopathy due to the early measurements of PT/INR and Thromboelastography (TEG) which will be performed on all enrolled subjects. TEG is an FDA approved tool; however, currently it is not standard of care

and only a small proportion of trauma centers across the country routinely obtain early PT/INR and point of care rapid-TEG analysis in the emergency department, soon after arrival in patients in hemorrhagic shock. Early recognition of coagulopathy for all enrolled subjects may lead to earlier interventions that improve clinical outcome.

For all participants in the trial, early and continual screening and assessment for clinical outcomes including multiple system organ failure (MSOF) and infection will occur and will have the potential to benefit all participants. It is the layering of standardization of pre-hospital resuscitation, early diagnosis of trauma induced coagulopathy and additional early assessment and screening for important clinical outcomes that highlights the benefits of participation in the PUPTH trial for both plasma and control arms of the study.

3 OBJECTIVES

3.1 Study Objectives

In this study, eligible patients with polytrauma (PTr) and major hemorrhage (MH) will be given either standard normal saline or TP in the pre-hospital setting.
The primary objective of this study is to compare the 30-day mortality between these two groups. If the patient is no longer hospitalized, this will be assessed with a follow-up phone call (see Appendix F for script).

The secondary objectives of this study are:

- to compare the blood pressure, pulse, temperature, lactate, total bicarbonate and pH between these groups upon emergency department arrival,
- to compare the cumulative utilization of blood products individually: units of red blood cells, units of plasma, doses of platelets (either apheresis unit or pooled dose of 3 to 4 units), doses of cryoprecipitate (one dose or pooled 6 units)], upon arrival to the hospital, 30 minutes after arriving, 8 hours after arriving and 24 hours after arriving between these two groups,
- to compare coagulation function (measured by thromboelastography, RoTEM, hemodyne, fibrinogen, factor V, factor VIII, pT, aPTT, von Willebrand's factor, D-dimer, PFA-100, platelet count and flow cytometry and lipidome testing (arachidonic acid metabolism, eicosinoids and prostocyclin expression) between these two groups, at baseline, at 30 minutes after arrival, at 8 hours after arrival and at 24 hours after arrival to the hospital,
- to compare hemoglobin/hematocrit between these two groups at baseline, at 30 minutes after arrival, at 8 hours after arrival and at 24 hours after arrival to the hospital,
- to compare rates of multi-system organ failure (MSOF), renal failure , number of days in the intensive care unit, number of days in the hospital, number of days on the ventilator, number of operations, and number of infections between these two groups.

3.2 Study Outcome Measures

3.2.1 Primary

Outcome variables including coagulation tests, hemodynamics, transfusion requirements, complications and survival will be described using means and standard deviation for normally distributed data and median with range for significantly skewed data. To describe the coagulation/ platelet response to PTr and the following 24 hours, repeated measures ANOVA will be used to detect significant changes in coagulation/platelet function over time. In order to identify important relationships, mixed model ANOVA and correlation analysis will be used to analyze coagulation/platelet function parameters in terms of: injury severity by ISS, tissue hypoperfusion by base deficit and lactate, transfusion, TIC (trauma-induced coagulopathy), and clinical outcome variables.

Indices of coagulation/platelet function will be used as independent variables in logistic regression analyses to ascertain their significance as predictors of relevant clinical outcomes including transfusion requirements, TIC, and survival to 30 days. Significant univariate

relationships will be further evaluated using multivariate regression adjusting for covariates including items such injury severity, shock severity, and transfusion utilization.
The specific interaction between injury severity and tissue hypoperfusion is found to be significantly related to coagulation function in trauma. In order to evaluate for interactions between the subgroups, mixed model two-way ANOVA will be used for four planned analyses. The combined effects of injury severity, tissue hypoperfusion, transfusions (such as massive transfusion protocols), and surgery numbers (as an effect modifier) on coagulation/platelet function will be determined as follows:

1. Injury severity by ISS quartile and presence or absence of tissue hypoperfusion by base deficit ≥ 6 and lactate ≥ 3.
2. ISS severity by GCS (Glasgow Coma Score, a measure of alertness) of 3-8 (severe), 9-12 (moderate), and 13-15 (mild). For each GCS category subjects will also be classified according to an anatomic descriptor based on neuro-imaging studies as having either: hemorrhage (hematoma, contusion, splenic or hepatic injury) vs. orthopedic injury.
3. GCS category by tissue perfusion category.
4. Volume and type of transfused blood products used (with and without activation of massive transfusion protocols) in order to highlight the effects of transfusion on platelet function.

At least 30 subjects in each ISS quartile, totaling 120 subjects, will be required to detect significant and relevant changes in coagulation/platelet function, including platelet contractile force, clot strength by TEG, aggregation, and thrombin generation with 80% power. A small pilot study described above of 35 TP subjects will be used initially to test coagulation/platelet protocols. Open enrollment will then take place to 100-200 subjects (following IRB approval and any additional community consultation/disclosure if required by the IRB). Interim analysis (every 50) will be performed in order to evaluate data quality and mitigate any risk to the study population. Open enrollment will then continue and will be capped at 210 subjects. An ISS of ≥15 will be used initially during enrollment to define poly-trauma.

3.2.2 Secondary

Injury Severity, Shock Severity, TIC, and Transfusion
In order to examine the effects of injury severity, shock severity, and TIC on coagulation/ platelet function during PTr, subjects will be categorized according to the following criteria for additional analysis:

- Injury Severity: The Injury Severity Score (ISS), which is an established method of estimating injury severity by both anatomic distribution and severity of individual injury, will be used to stratify subjects into quartiles for comparison. An ISS of >15 indicates severe injury and coincides with a sharp increase in mortality and will therefore be used as the lower limit to define poly-trauma. This definition will preclude multiple minor injuries such as contusions and lacerations that would not truly represent PTr/MH while still including the severely injured. Similar comparisons have been made between ISS and plasma-phase coagulation function in trauma and will therefore facilitate comparison of our results to published literature. Injury Severity Score will be calculated by standard algorithm and will be updated each time blood samples are drawn as injuries are discovered and in order to account for evolving injury. Full knowledge of all injures is required to accurately calculate ISS. In many cases it is expected that all injuries will not be readily identified upon initial

patient evaluation leading to inclusion of mildly injured subjects that do not fit the criteria of PTr. Therefore, initial inclusion will be based on risk of PTr by hemodynamics and known injury at the time of arrival.

- Shock Severity: Two redundant biochemical markers of shock severity or tissue hypoperfusion will be used to classify subjects. The use of lactate and base excess, while imperfect, are the standards used for the initial assessment of tissue hypoperfusion in the patient of PTr. A base deficit of ≥6 by blood gas (routinely collected) analysis will be used to identify the presence of hypoperfusion. Base deficit will be corroborated by a blood lactate concentration of ≥ 3 mmol/l in order to verify the shock state. Those subjects meeting both criteria will be classified as having tissue hypoperfusion. These measurements are more predictive for significant tissue hypoperfusion than hemodynamic variables such as blood pressure and the use of both base deficit and lactate will add much-needed redundancy to the estimate of shock severity. Subjects will be divided according to presence or absence of tissue hypoperfusion and coagulation and platelet function will be compared in these two subgroups. In addition, presence or absence of tissue hypoperfusion will be used as a covariate when examining the relationship between ISS and coagulation/platelet function. One would expect the degree of hypotension to be less in patients receiving TP.

4 STUDY DESIGN

4.1 Study Overview

1. Preclinical preparations:
    a. Community consultation and education
    b. Quality control checks on blood product refrigerators to be used
    c. Training of EMS personnel in the proper handling and administration of TP and in the recognition of adverse reactions due to TP infusion
    d. EMS supervisor obtains 2 units of group A TP (anti-B titer < 1:100) from Virginia Commonwealth University Medical Center (VCUMC) Blood Bank personnel
2. EMS supervisor arrives on the trauma scene and identifies patient fitting inclusion/exclusion criteria for the PUPTH study
3. EMS Supervisor calls VCUMC emergency department and speaks with study physician to confirm patient's eligibility. Meanwhile, attempts are made to elicit refusal to participate in the study from the patient or legally authorized representative (LAR) / next of kin while other EMTs on the scene work to stabilize patient and secure IV access
4. If the patient is enrolled in the study and randomized to receive TP, the EMS supervisor initiates the TP infusion after the first set of tubes for coagulation/lipid testing is drawn. If the patient is randomized to receive normal saline, the first set of coagulation tubes is drawn and the patient continues to receive standard normal saline therapy
5. EMTs tend to the patient as necessary, monitor vital signs and monitor for signs of any adverse reactions to the TP
6. As soon as possible, the patient is transported to the VCUMC emergency department. (the patient may still be receiving plasma during the transport)
7. The patient is evaluated upon his/her arrival to the VCUMC emergency department as is standard care
8. Thirty minutes after arrival (after the patient has been stabilized), the next set of laboratory tests are drawn
9. The study coordinator begins attempts to explain the study to and obtain consent to continue the study from the patient or LAR/next of kin
10. Additional laboratory tests are drawn at 8 hours and 24 hours after hospital arrival
11. The study patients receive standard therapy while hospitalized at VCUMC
12. Demographic, clinical data and morbidity and mortality outcomes are identified in the patient's medical record and recorded on de-identified study forms.

5 STUDY ENROLLMENT AND WITHDRAWAL

At least 30 subjects in each ISS quartile, totaling 120 subjects, will be required to detect significant and relevant changes in coagulation/platelet function, including platelet contractile force, clot strength by TEG, aggregation, and thrombin generation with 80% power. The study will draw from two of the large civilian EMS systems served by Virginia Commonwealth University Medical Center (VCUMC), an American College of Surgeons certified Level 1 Trauma center. The city of Richmond EMS system (Richmond Ambulance Authority) serves a metro area of 222,000 and provides over 27,000 EMS transports per year. The county of Henrico and its EMS system (Henrico Fire EMS) will also be used. This system serves a population of 325,000 and makes over 30,000 transports per year. In 2010, VCUMC trauma center had 3807 trauma activations. Massive transfusion protocols (see IND Appendix 6) are used in over 70 subjects per year.

5.1 Subject Inclusion Criteria

1. ≥18 yo.
2. Blunt or penetrating trauma
3. Either sex
4. BP systolic ≤70 mmHg or BP 70-90 mmHg with HR ≥108 BPM
5. Major on-going hemorrhage with unstable vital signs consistent with above
6. If the patient is lucid and able to refuse, but doesn't; if patient is unable to give consent, but legally authorized representative (LAR)/adult next of kin is able to be consulted and they do not refuse the study; if patient is unable to give consent and no LAR/adult next of kin available, exception from informed consent (EFIC) and patient included in study

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Wearing an opt out wrist band
   Having a wallet card or wearing medical alert jewelry/bracelet, etc. found to indicate Jehovah's Witness or similar with objections to blood transfusions
2. Refusal to participate (by patient or LAR/next of kin)
   Communication barrier at the time of eliciting refusal (non-English or non-Spanish speaking)
3. Not expected to survive transport to VCUMC
4. Documented "Do not resuscitate" (DNR) order found/known to exist
5. Cardiac arrest or CPR prior to randomization
6. Penetrating head trauma
7. Age<18 years old
8. Known/obvious pregnancy
9. Prisoner
10. Arrival by EMS supervisor at the time ambulance transport is underway
11. Inability to obtain IV access to administer TP
12. Patients with burns (fire, scald, chemical or otherwise) of >20% of body surface will be excluded.

5.3 Strategies for Recruitment and Retention

5.3.1 Subjects will be enrolled (most often) without informed consent. If they fit inclusion criteria and are poly-trauma patients encountered within Henrico County and/or Richmond City (by Henrico Fire or RAA EMS; no volunteer rescue squads will participate in the study) then they will be considered for inclusion in the study.

5.3.2 EMS supervisors will screen patients (fitting shock, blood loss and vital sign criteria), check with the study physician on call by radio or phone and if given a direct order by that physician the subjects will be randomized to saline (control) v. TP resuscitation. While highly unlikely at the scene of a trauma, if a patient or LAR/adult next of kin can understand the study, EMS will provide information about the study to the appropriate individual and a refusal to participate will be sought. If participation is refused, nothing further for the study will occur and the patient will receive standard of care by EMS and VCUHS.

5.3.3 Once on site at VCUHS the study coordinator, will see the LAR or adult next of kin and provide information and seek consent for the patient to participate/continue in the study", subsequent blood draws and use of hospital records for following information noted in section C directly above.

5.3.4 If a patient is discovered to be pregnant, under 18 years of age or prisoner, at the time of discovery, s/he will be withdrawn from the study and the IRB notified of a protocol deviation (according to IRB policy). Explanation will be given to the (former) subject (if conscious in VCUHS) or the LAR/adult next of kin of the withdrawal. Data will be used until the time of withdrawal but no other data will be collected and the subject will no longer be followed.

5.4 Study Activation

5.4.1 The EMS Supervisor will contact the VCUMC Transfer Center at either (804) 828-2638 or 1 866-628-9337 stating: "I have a potential Pre-Hospital Plasma Study subject and need to talk with the study physician on call."

5.4.2 The Transfer Center Representative will page or call the study physician on call for the PUPTH study. If no response within 3 minutes, the backup physician will be called. The Transfer Center Representative remains on the line with the EMS Supervisor and the Study Physician until the call is completed.

5.5 Treatment Assignment Procedures

5.5.1 The Study physician will determine if the subject is eligible for enrollment after speaking with the EMS Supervisor. If the patient is deemed not eligible, The Transfer Center representative will record the subject as a screen failure.

5.6 Randomization Procedures

5.6.1 If the patient is deemed eligible for enrollment, the Transfer Center representative will then activate a "Pre-hospital plasma study alert," open a randomization envelope and inform the EMS Supervisor in which arm the patient is enrolled, making note of the study entry on the randomization sheet.

5.7 Subject Withdrawal

5.7.1 If a subject dies before consent is obtained from the patient or LAR, the treating trauma surgeon (all are investigators in the trial), will inform the family members/LAR about the patient's enrollment in the PUPTH trial and answer any questions they may have when they meet with the family to discuss his/her condition.

5.7.2 If the patient does not want to continue in the study or the LAR/next of kin does not want the patient to continue in the study, the patient will be withdrawn from the trial.

5.7.3 Withdrawal will not change the patient's further care in any way. There will be no medical, social, or billing implications for a patient taking part in the study or for a patient withdrawing from it.

5.7.4 Once in the ED, the patients (or research subjects) will receive transfusions, on-going volume resuscitation, surgery, ICU care at the direction of the trauma surgery and ED services. Those research subjects in the trial will have extra blood drawn for research lab investigations of coagulation, inflammation, and lipids profile. In addition, de-identified data regarding the research subject's demographics, clinical course (from the medical record) and outcome will be recorded in a research form. If a research subject is withdrawn from the trial, no further research coagulation/inflammation laboratory blood draws will occur. However, since that subject has been randomized to receive either NS or TP their (de-identified) clinical data and outcomes will be entered into the study records.

5.7.5 Reasons for Withdrawal

5.7.5.1 Subjects or their LAR are free to withdraw from participation in the study at any time upon request.

5.7.5.2 An investigator may terminate a study subject's participation in the study if any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

5.7.5.3 An investigator may terminate a study subject's participation in the study if the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.7.6 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

5.7.6.1 No additional contact or data collection will occur after a patient or LAR has withdrawn from the study. Only data collected previously while the patient or LAR had consented or while the waiver of consent still applied can be used.

5.7.7 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause.

5.7.7.1 Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigator, DoD, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

5.7.7.2 Circumstances that may warrant termination include, but are not limited to: determination of unexpected, significant, or unacceptable risk to subjects, insufficient adherence to protocol requirements, data that are not sufficiently complete and/or evaluable, and determination of futility.

6 STUDY INTERVENTION

6.1 Study Product Description

Two units of thawed A positive plasma are carried in electric blood coolers by one supervisor for Richmond Ambulance Authority and one supervisor for Henrico County Fire/EMS. Trauma patients meeting study eligibility will be randomly selected to receive plasma in the field.

The Transfusion Service has a mechanism to verify acceptability of plasma prior to issue and assign to study patients. Records are maintained to capture all successive steps in the processing, storage, and distribution of blood products. Unused plasma is returned daily to Transfusion Medicine by the EMS supervisors. Returned units are evaluated for specific criteria, including bag integrity, temperature indicator status and data logger temperatures. If found acceptable, units are returned to the general plasma inventory for reissue within VCU Medical Center. If unacceptable, plasma units are destroyed.

SOPs for the storage and dispense of blood products can be found in Appendix B.

6.2 Preparation/Maintenance of Blood Products/Intervention

6.2.1 At a maximum of once every 24 hours, the EMS supervisors for Richmond Ambulance Authority (RAA) and Henrico county EMS (HC-EMS) will restock the study refrigerators on their supervisors' vehicles with 2 units of group A TP (anti-B titer < 1:100). At no time will the EMS supervisor carry more than 2 units of TP and at no time will the TP be out of the VCUMC blood bank for more than 24 hours.

6.2.2 The EMS supervisor will contact the VCUMC blood bank when they are coming into the ED. The TP will be dispatched by blood bank personnel and directly placed in the refrigeration unit under blood bank supervision. Appropriate paperwork and electronic records will be signed (see Assigning, Issuing and Returning study plasma, IND Appendix 6).

6.2.3 The refrigeration units will be kept locked (electronic code required for opening) and electronic records will be created for whenever that refrigeration unit is opened. It should only be opened to either re-stock or retrieve TP for study patients

6.2.3.1 Opening the refrigerator for any other activity will constitute a protocol violation and a written explanation of that event will be required.

6.2.4 Units of TP not infused at trauma sites will be returned (within the 24-hour window) to the VCUMC blood bank. These returned units of TP will be inspected thoroughly by blood blank personnel.

6.2.4.1 Units not infused, after certification of their maintenance at correct temperature (1-6°C), will be returned into the net utilization for distribution to patients at need within the

hospital. The usage of TP will be recorded as will the usage of other blood products in the study subjects.

6.2.5 The refrigeration unit temperature records and quality control data will also be analyzed to ensure that the TP was maintained at all times within the mandated temperature range of 1 – 6^0 C (see Assigning, Issuing and Returning study plasma, IND Appendix 6).

6.2.6 As explained in the introductory statement and background section (IND page 4 and pages 21-22) the products that will be used in this study (collectively referred to as "TP" in this document) are thawed fresh frozen plasma (FFP), thawed plasma frozen within 24 hours (PF24) and thawed plasma (thawed FFP and thawed FP24 must be renamed "thawed plasma" after they have been in a thawed state for over 24 hours). Whichever of these products that is available in the VCUMC blood bank at the time of the EMS supervisor's arrival will be the product that is transferred to the supervisor's vehicle.

6.2.7 All of the TP used in this study will be group A, with an anti-B titer of less than 1:100 (see TP titer procedure in IND Appendix 6).

6.2.8 TP will be maintained at all times under conditions as stipulated by the FDA and within guidelines of the AABB (formerly the American Association of Blood Banks; now the full name for the not-for-profit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies).

6.3 Administration of Intervention

6.3.1 On their arrival to the site of an EMS call for a PTr/MH patient, the EMS supervisor will assess the vital signs and groups of injuries of the patient. For those patients fitting the wide inclusion criteria of the PUPTH study, the supervisor will radio and speak with the appropriate study physician on call (identified trauma surgery or ED attending) for the study.

6.3.2 The physician taking call will discuss with the on-site EMS supervisor the nature of the injuries and likelihood of the patient surviving transport to VCUMC-ED. That study on-call doctor will then authorize (or not) the use of the TP and enrollment into the study.

6.3.3 All other EMS providers on site will commence routine therapy (IV establishment and NS infusion) prior to the arrival of the EMS supervisor. In no way should the existence of the PUPTH protocol slow down or otherwise alter the extraction, or early treatment of a PTr/MH patient.

6.3.4 If two patients at the scene fit criteria, the first patient to have IV lines placed will be enrolled in the study.

6.3.5 The EMS supervisor will be responsible for unlocking the TP refrigerator, and he/she will initiate the transfusion of that blood product to the research subject. Either the supervisor or a qualified responder will continue the administration of the blood product.

6.3.5.1 One unit of TP will be administered through a dedicated IV line as quickly as possible, followed by the second unit. This will be administered through the largest available IV line (large bore IV) able to be started by EMS. Gravity feed without external pressure will be the method of in-flow in accordance with AABB guidelines. The EMS can run saline or other non-study drugs that they are allowed to carry but only when the TP is NOT running. The line is dedicated to the TP transfusion only during the administration of TP. If only one IV can be obtained, saline would have been started until subject enrolled.

6.3.5.2 Then, if the subject were to receive TP, over the next few minutes TP would be administered and when TP finished running, saline would be restarted (or subject would already be at VCUMC and standard of care in the trauma bay would commence).

6.3.6 Blood for the study will be drawn from a peripherally accessed vein.

6.3.7 Vital signs will be recorded every 5 minutes at a minimum, as is standard practice for EMS. Other life support medications will be administered in accordance with standard BLS/ACLS guidelines and under the direction of the EMS structure and the radio communicating ED doctors.

6.3.8 If the research subject responds to TP and improves his/her systolic blood pressure that may well obviate the use of more NS by EMS and the ED directing physicians.

6.3.9 Research subjects randomized to TP or NS portions of the trial must be transported to VCUMC. It is the medical director of each EMS service who has ultimate authority for transport destination. It will be a standing order of this trial that any time an EMS supervisor enters a research subject into the trial, the subject must go to VCUMC-ED.

6.3.9.1 The only reason to stop a transport on its way would be for unexpected loss of the airway in the process of the transport. If this were to happen, and a research subject had been entered into the PUPTH trial the EMS personnel would find the closest ED, get an airway (surgical perhaps) reestablished and continue transport to VCUMC-ED.

6.3.10 On entry to the VCUMC-ED the research subjects will receive resuscitation fluids as deemed appropriate by the physician in charge of their care. This fluid resuscitation could (but does not necessarily) include more plasma, in addition to packed red cells, cryoprecipitate, platelet infusions and or NS, other colloids (albumin/Hextend) or other fluids the medical team determines to be appropriate. No pre-determined branching treatment tree will exist for PUPTH research subjects once they have entered the VCUMC-ED.

6.4 Procedures for Training Interventionists and Monitoring Intervention Fidelity

6.4.1 Identical training materials will be provided for both EMS agencies. These materials can be found on an electronic shared study dive and consist of power point presentations, mock drills, handouts, and tip sheets.

6.4.2 Each EMS agency (RAA and Henrico Fire) will maintain at their location a roster of employees engaged in the research. This includes those individuals designated on each VCU-EMS organization agreement as Principal Investigator (PI) for that agency as well as supervisors and those who ride in ambulances who definitely will or possibly might be involved in the administration of plasma to a study subject.

6.5 The VCU Study Coordinator/IRB Liaison will maintain on the VCU shared drive (accessible only to VCU study personnel) additional VCU IRB documents named for each agency. VCU IRB Personnel Information and Change forms as well as VCU IRB Study Personnel Rosters for each agency will contain the name of the agency, agency PI (for VCU purposes, their role will be as sub-Investigator) and all supervisors engaged in the research.

6.5.1 Rosters will be updated as necessary in the same manner as other VCU IRB personnel documentation when there are personnel changes.

6.5.2 The Study Coordinator will maintain an electronic copy of the completed CITI certificates for all of these individuals. No other EMS personnel documentation will be maintained at VCU.

6.6 All EMS personnel identified as engaging in the research will be trained as described in section 6.9 of this SOP. Records of the individuals trained will be maintained by each of the agencies at their location.

6.7 Richmond Ambulance Authority (RAA) Training Documentation

6.7.1 Documentation of education by RAA is maintained on a computer generated system that will require the EMS personnel to LOG ON with USER NAME and PASSWORD (that serves as their electronic signature) to view education specific to this study as well as documentation of CITI training. The computer captures date, time, employee name and education modules completed. Educational modules include a power point presentation of PUPTH standard operating procedures (SOP) for EMS personnel, the safe handling of plasma, side effects and transfusion reactions to be looking for and recording, and any other training deemed necessary during the course of the study.

6.8 Henrico Fire Training Documentation

6.8.1 Learner specifics will be recorded on a spreadsheet created by the EMS supervisor with columns documenting the following: EMS personnel name, Date educational module began, name of Program being viewed (e.g. CITI training, SOP, Handling of Plasma), Signature and Date completed

6.9 Procedures for Training of Clinicians on Procedural Intervention

6.9.1 Training developed with complete details for each study-specific responsibility (including but not limited to those for EMS, EMS supervisors, study coordinators, investigators and any other job) and IRB will be and remain approved by the VCU IRB.

6.9.2 Training dealing with medical issues will be under the guidance of one of the physician investigators.

6.9.3 Blood banking issues will be under the direction of Dr. Sanford.

6.9.4 One of the investigators or study coordinators &/or (following a Train-the-Trainer) EMS training staff will train EMS on remaining specifics of the study.

6.9.5 One of the study coordinators will train VCU/VCUHS study personnel on (non-medical) specifics of the study.

6.9.5.1 It will be part of the training for the EMS supervisors that the importance of searching for such a "do not transfuse" card and documenting that this search was performed will be emphasized.

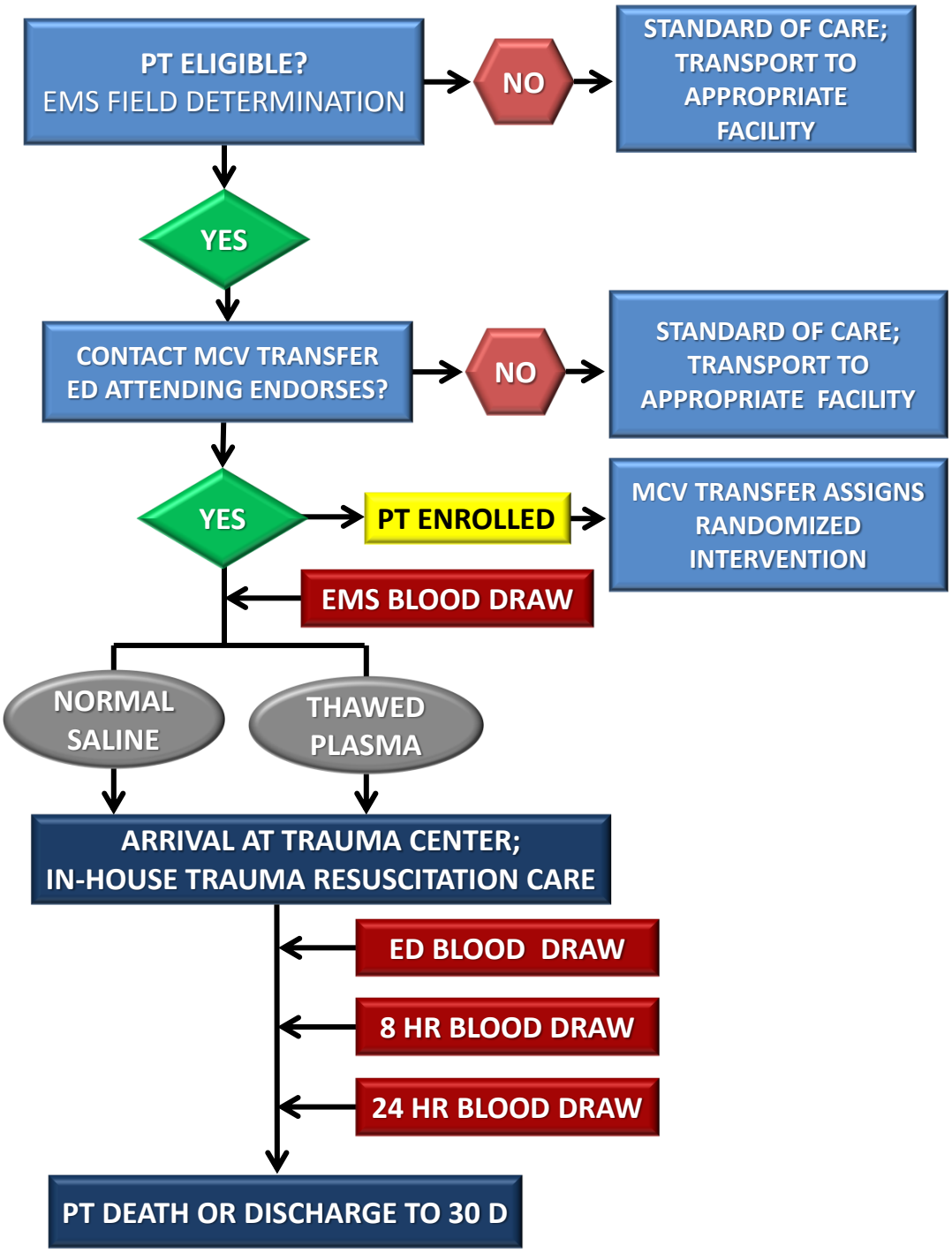
6.10 Assessment of Clinician and/or Subject Compliance with Study Procedural Interventions

6.10.1 EMS Supervisors will oversee and ensure the compliance of EMS personnel at both EMS organizations.

6.10.2 EMS personnel and VCUHS licensed study personnel will ultimately be governed by and expected to comply with their respective licensing organization (Old Dominion EMS Alliance, VA Board of Nursing, etc.).

6.10.3 Study coordinators, the PI, and study physicians will ensure compliance and adherence to protocol for activities conducted at VCUHS.

7 STUDY SCHEDULE



7.1 Screening

7.1.1 EMS supervisor arrives on the trauma scene and identifies patient fitting inclusion/exclusion criteria for the PUPTH study. EMS Supervisor calls VCUMC emergency department and speaks with study physician to confirm patient's eligibility. Meanwhile, attempts are made to elicit refusal to participate in the study from the patient or legally authorized representative (LAR)/next of kin while other EMTs on the scene work to stabilize patient and secure IV access.

7.2 Enrollment/Baseline

7.2.1 If the patient is enrolled in the study and randomized to receive TP, the EMS supervisor initiates the TP infusion after the first set of tubes for coagulation/lipid testing is drawn. If the patient is randomized to receive normal saline, the first set of coagulation tubes is drawn and the patient continues to receive standard normal saline therapy.

7.2.2 Upon enrollment into the trial and immediately prior to infusion of TP, four vacutainer tubes (one EDTA purple 5 mL and two citrate blue top 5 mL and a 5 mL specialized tube from VCURES coagulation laboratory; total volume 20 mL) will be drawn and transported at room temperature to the ED with the research subject. Those tubes will be transported by EMS and handed off to the study team member in the ED for immediate transfer to the VCURES coagulation laboratory.

7.3 Study Procedures/Evaluations

7.3.1 Another set of blood samples will be drawn thirty minutes after VCUMC-ED arrival (this time is chosen because within the first 30 minutes efforts will be being made to stabilize, resuscitate, diagnose and triage the patient, and blood samples for research will be of less importance than these other clinical priorities). Blood samples (same number, groups of tubes, and volumes) will be drawn at intervals after ED arrival (30 minutes, 8 hours and 24 hours) for a total amount of 80 mL for the entire study. Normal saline PTr/MH subjects will receive normal saline in the field and during transport as per routine.

7.3.2 Patient demographics (age, weight, height, past medical history, medications, ISS) will be gathered from the medical record as they become available after admission. Hemodynamics, transfusion utilization, time in ICU, operations, hospital length of stay, infections, will all be gathered from hospital charting. Hemoglobin/Hct (hematocrit), platelet counts will be recorded and compared between groups at the conclusion of the 30 day study period.

7.4 Laboratory Procedures/Evaluations

7.4.1 Specimen Preparation, Handling, and Storage

7.4.1.1 Upon enrollment into the trial and immediately prior to infusion of TP, four vacutainer tubes (one EDTA purple 5 mL and two citrate blue top 5 mL and a 5 mL specialized tube from VCURES coagulation laboratory; total volume 20 mL) will be drawn and transported at room temperature to the ED with the research subject. Those tubes will be transported by EMS and handed off to the study team member in the ED for immediate transfer to the VCURES coagulation laboratory.

7.4.1.2 Another set of blood samples will be drawn thirty minutes after VCUMC-ED arrival (this time is chosen because within the first 30 minutes efforts will be being made to stabilize, resuscitate, diagnose and triage the patient, and blood samples for research will be of less importance than these other clinical priorities).

7.4.1.3 Coagulation testing will include thromboelastography, RoTEM, hemodyne, fibrinogen, factor V, factor VII, PT, INR, aPTT, thromboelastography (TEG) von Willebrand's factor, D-Dimer, PFA-100 and platelet count and flow cytometry.

8 ASSESSMENT OF SAFETY

Study progress and safety will be reviewed weekly by the Safety Oversight Officer. Progress reports including patient recruitment, retention/attrition, and AE/SAE will be provided to the independent study monitors. All adverse events will be assessed for relationship to the study intervention. Reporting forms will be submitted to the Data Safety Monitoring Board (DSMB). This is done in accordance by human subjects research guidelines set forth by the US Military Army Materiel Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Regulatory Requirements (see Appendix H).

8.1 It is recommended that the DSMB meet as often as necessary but at least twice yearly to examine the accumulated safety and enrolment data, review study progress, and discuss other factors (internal or external to the study) that might impact continuation of the study as designed.

8.1.1 A DSMB meeting may be requested by DSMB members, DoD, IRB, or study Principal Investigator at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the Program Officer and DSMB Chair.

8.1.2 In the event a DSMB member cannot attend a meeting, in person or by conference call, they may receive a copy of the closed session DSMB report and provide written comments to the DMSB Chair for consideration at the meeting.

8.2 Adverse Events

Adverse event: any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product and which may or may not have a causal relationship with the treatment. (21 CFR part 312).

8.2.1 All reported adverse events felt to be associated with the research intervention will be reviewed as to treatment arm and further classified by: a) severity (serious or non-serious); and b) expected vs. unexpected.

8.2.2 The SAE will be recorded on the subject's AE/SAE log.

8.2.3 Adverse Events will be attributed as follows:

1. Unrelated: The AE is clearly not related to the intervention categories
2. Unlikely: The AE is doubtfully related to the intervention
3. Possible: The AE may be related to the intervention
4. Probable: The AE is likely related to the intervention
5. Definite: The AE is clearly related to the interventions

8.3 Unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.1 Other types of incidents, experiences, and outcomes that are not considered adverse events are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

8.3.2 All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

8.3.3 This study is conducted under an IND and will comply with mandatory reporting of safety events to the Food and Drug Administration (FDA) regulations found in 21 CFR 312.32 Events of Special Interest.

8.4 Time Period and Frequency for Event Assessment and Follow-Up

8.4.1 Unanticipated problems will be recorded in the data collection system throughout the study.

8.4.2 The PI will record using a CRF all reportable events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation.

8.4.3 Events will be followed for outcome information until resolution or stabilization.

8.5 Characteristics of an Adverse Event

8.5.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Unrelated The AE is clearly not related to the intervention

2. Unlikely The AE is doubtfully related to the intervention
3. Possible The AE may be related to the intervention
4. Probable The AE is likely related to the intervention
5. Definite The AE is clearly related to the interventions

8.5.2 Expectedness of SAEs

8.5.2.1 The independent safety monitor and the Study PI will be responsible for determining whether an SAE is expected or unexpected.

8.5.2.2 An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.5.3 Severity of Event

8.5.3.1 AEs will be labeled according to the severity that is based on the impact of the subject. An AE will be termed “mild” if it does not have a major impact on the subject, “moderate” if it causes the subject some minor inconvenience and “severe” if it causes a substantial disruption to a subject’s wellbeing.

8.5.3.2 A serious adverse event (SAE) is any untoward medical occurrence that results in any one of the following outcomes: death, be a life threatening event, inpatient hospitalization or prolongation of existing hospitalization, a congenital anomaly or birth defect, any other condition that investigators judge as representing a significant hazard.

8.6 Reporting Procedures

8.6.1 Study progress and safety will be reviewed weekly by the Safety Oversight Officer.

8.6.2 Progress reports including patient recruitment, retention/attrition, and AE/SAE will be provided to the independent study monitors. All adverse events will be assessed for relationship to the study intervention. Reporting forms will be submitted to the Data Safety Monitoring Board (DSMB). All reported adverse events felt to be associated with the research intervention will be reviewed as to treatment arm and further classified by: a) severity (serious or non-serious); and b) expected vs. unexpected. The study population is expected to have a large number of unrelated, expected serious adverse events including death from trauma related injuries. The SAE will be recorded on the subject's AE/SAE log.

8.6.3 VCUMC blood bank will provide donor 'A+' thawed plasma and will follow the AABB guidelines (current standard of practice) for blood banks. Any transfusion reaction occurring to any subject that receives plasma supplied from the VCUMC blood bank, whether in the pre-hospital setting during transport or throughout a patient's admission, will be investigated and reported according to the blood bank protocol.

8.7 Halting Rules

8.7.1 It is expected that the trial will terminate when the intended sample size has been achieved. However, the trial will be stopped prior to completion if: (1) at n=70, the

Farrington and Manning z-score exceeds 3.49 in absolute value; (2) at n=140, the z-score exceeds 2.46 in absolute value [27, 28]; (3) the intervention is associated with adverse effects that call into question the safety of the test intervention; (4) problems with study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (5) any new information that becomes available during the trial necessitates discontinuation of the trial.

8.7.2 The PI will include an assessment of futility in the annual progress report to the FDA (using statistical means such as predictive probability, if appropriate) and will consult with the Data and Safety monitoring Board (DSMB) to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

9 STUDY OVERSIGHT

9.1 In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in appropriate clinical, statistical, scientific, ethical disciplines.

9.2 A second-in –command PI will be assigned if the PI, Dr. Bruce Spiess is unable to be available for during enrollment. This co-investigator is Dr. Christopher Hogan.

9.3 This group will be charged with independently examining data every 25 patients to assure safety. If the DSMB reviews the data at any time and feels that there is a statistical significant difference between TP or NS or even a safety concerning trend they will have the ability to stop enrollment in the study. They may stop the study if they feel the conduct of the study is unethical because the use of TP is providing a survival benefit or other major improvement in clinical outcome as well as they could stop the study if TP demonstrates increased patient risk.

9.4 The DSMB will operate under the rules of an IRB-approved charter. Elements that the DSMB needs to assess will be clearly defined. The signed charter will kept on file on the shared study drive by the SC.

9.5 DSMB members should not have any competing interests.

9.5.1 Competing interests are considered:

- Serving as a part-time, full-time, paid, or unpaid employee of any organizations that are involved in the study under review,
- Whose products or services will be used or tested in the study under review, or
- Whose products or services would be directly and predictably affected in a major way by the outcome of the study;
- Serving as an officer, member, owner, trustee, director, expert advisor, or consultant of such organizations;
- Having financial interests or assets – of the member's own or those of my spouse, dependent children, or organizations with which he/she is connected – in any organizations meeting the above criteria.

9.5.2 DSMB Members will notify the Principal Investigator and SC promptly if a change occurs in any of the members' financial interests during the tenure of a member's responsibilities, or DSMB member discovers that an organization with which he/she has a relationship meets the criteria for a competing interest.

9.5.3 DSMB members will not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest.

9.6 DSMB members are responsible for maintaining the confidentiality of any non-public information that they receive or become aware of through this activity and will avoid using such information for his/her personal benefit, the benefit of his/her associates, or the benefit of organizations with which he/she is connected or with which he/she has financial involvement.

9.7 In addition to the PI's responsibility for oversight, study oversight will be under the direction of an Independent Safety Monitor (ISM), Dr. Ronsard Daniel. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues, as further explained in Section 10 of this SOP.

10 CLINICAL SITE MONITORING

10.1 In addition to the DSMB, Dr. Ronsard Daniel will function within the institution as the clinical safety oversight person/research monitor/medical monitor, hereunto referred to as "independent safety monitor."

10.2 The independent safety monitor must review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the US Army Human Research Subject Protections Office.

10.3 The independent safety monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research.

10.4 The independent safety monitor shall have authority to stop the research in progress, remove individual human subjects from the research, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report.

10.5 The independent safety monitor shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the US Army Human Research Subject Protections Office.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

11.1.1 The primary hypothesis is that the cohort of patients with polytrauma and major hemorrhage that receives TP in the pre-hospital setting will have lower 30-day mortality than the group that receives standard pre-hospital therapy (normal saline).

11.1.2 Following are the secondary hypotheses:

- The group receiving TP will exhibit superior vital signs, lower lactate level, higher bicarbonate and higher pH levels than the group receiving normal saline.
- The group receiving TP will require fewer blood products (red blood cells, plasma, platelets and cryoprecipitate) than the group receiving normal saline.
- The group receiving TP will exhibit a superior coagulation state (as measured by thromboelastography, RoTEM, hemodyne, fibrinogen, factor V, factor VIII, PT, aPTT, von Willebrand's factor, D-dimer, PFA-100, platelet count and flow cytometry) than the group receiving normal saline.
- The group receiving TP will show reduced levels of oxidative stress on the lipidome/metabalome (measured by arachidonic acid metabolism, eicosinoids and prostocyclin expression) compared to the group receiving normal saline.
- The group receiving TP will have higher hemoglobin/hematocrit than the group receiving normal saline
- The group receiving TP will have lower rates of multisystem organ failure, lower rates of renal failure, stay fewer days in the intensive care unit, be on the ventilator for fewer days, and have shorter hospital stays, fewer infections and fewer operations than the group receiving normal saline.

11.2 The sample size will contain at least 30 subjects in each ISS quartile, totaling 120 subjects, will be required to detect significant and relevant changes in coagulation/platelet function, including platelet contractile force, clot strength by TEG, aggregation, and thrombin generation with 80% power. A small pilot study described above of 35 TP subjects will be used initially to test coagulation/platelet protocols. Open enrollment will then take place to 100-200 subjects (following IRB approval and any additional community consultation/disclosure if required by the IRB). Open enrollment will then continue and will be capped at 200 subjects. An ISS of ≥15 will be used initially during enrollment to define poly-trauma.

11.3 Interim analysis (every 50 subjects) will be performed in order to evaluate data quality and mitigate any risk to the study population.

11.4 Safety analysis will be performed by the DSMB every 25 patients. If the DSMB reviews the data at any time and feels that there is a statistical significant difference

between TP or NS or even a safety concerning trend they will have the ability to stop enrollment in the study. They may stop the study if they feel the conduct of the study is unethical because the use of TP is providing a survival benefit or other major improvement in clinical outcome as well as they could stop the study if TP demonstrates increased patient risk.

11.5 Final Analysis Plan

11.5.1 Outcome variables including coagulation tests, hemodynamics, transfusion requirements, complications and survival will be described using means and standard deviation for normally distributed data and median with range for significantly skewed data. To describe the coagulation/ platelet response to PTr and the following 24 hours, repeated measures ANOVA will be used to detect significant changes in coagulation/platelet function over time. In order to identify important relationships, mixed model ANOVA and correlation analysis will be used to analyze coagulation/platelet function parameters in terms of: injury severity by ISS, tissue hypoperfusion by base deficit and lactate, transfusion, TIC (trauma-induced coagulopathy), and clinical outcome variables.

11.5.2 Indices of coagulation/platelet function will be used as independent variables in logistic regression analyses to ascertain their significance as predictors of relevant clinical outcomes including transfusion requirements, TIC, and survival to 30 days. Significant univariate relationships will be further evaluated using multivariate regression adjusting for covariates including items such injury severity, shock severity, transfusion utilization.

11.5.3 The specific interaction between injury severity and tissue hypoperfusion has been found to be significantly related to coagulation function in trauma. In order to evaluate for interactions between the subgroups, mixed model two-way ANOVA will be used for four planned analyses. The combined effects of injury severity, tissue hypoperfusion, transfusions (such as massive transfusion protocols), and surgery numbers (as an effect modifier) on coagulation/platelet function will be determined as follows:

1. Injury severity by ISS quartile and presence or absence of tissue hypoperfusion by base deficit ≥ 6 and lactate ≥ 3.

2. ISS severity by GCS (Glasgow Coma Score, a measure of alertness) of 3-8 (severe), 9-12 (moderate), and 13-15 (mild). For each GCS category subjects will also be classified according to an anatomic descriptor based on neuro-imaging studies as having either: hemorrhage (hematoma, contusion, splenic or hepatic injury) vs. orthopedic injury.

3. GCS category by tissue perfusion category.

4. Volume and type of transfused blood products used (with and without activation of massive transfusion protocols) in order to highlight the effects of transfusion on platelet function.

11.5.4 Subgroup Analysis

11.5.4.1 In order to examine the effects of injury severity, shock severity, and TIC on coagulation/ platelet function during PTr, subjects will be categorized according to the following criteria for additional analysis:

1. Injury Severity: The Injury Severity Score (ISS), which is an established method of estimating injury severity by both anatomic distribution and severity of individual injury, will be used to stratify subjects into quartiles for comparison. An ISS of >15 indicates severe injury and coincides with a sharp increase in mortality and will therefore be used as the lower limit to define poly-trauma. This definition will preclude multiple minor injuries such as contusions and lacerations that would not truly represent PTr/MH while still including the severely injured. Similar comparisons have been made between ISS and plasma-phase coagulation function in trauma and will therefore facilitate comparison of our results to published literature. Injury Severity Score will be calculated by standard algorithm and will be updated each time blood samples are drawn as injuries are discovered and in order to account for evolving injury. Full knowledge of all injures is required to accurately calculate ISS. In many cases it is expected that all injuries will not be readily identified upon initial patient evaluation leading to inclusion of mildly injured subjects that do not fit the criteria of PTr. Therefore, initial inclusion will be based on risk of PTr by hemodynamics and known injury at the time of arrival.

2. Shock Severity: Two redundant biochemical markers of shock severity or tissue hypoperfusion will be used to classify subjects. The use of lactate and base excess, while imperfect, are the standards used for the initial assessment of tissue hypoperfusion in the patient of PTr. A base deficit of ≥6 by blood gas (routinely collected) analysis will be used to identify the presence of hypoperfusion. Base deficit will be corroborated by a blood lactate concentration of ≥ 3 mmol/l in order to verify the shock state. Those subjects meeting both criteria will be classified as having tissue hypoperfusion. These measurements are more predictive for significant tissue hypoperfusion than hemodynamic variables such as blood pressure and the use of both base deficit and lactate will add much-needed redundancy to the estimate of shock severity. Subjects will be divided according to presence or absence of tissue hypoperfusion and coagulation and platelet function will be compared in these two subgroups. In addition, presence or absence of tissue hypoperfusion will be used as a covariate when examining the relationship between ISS and coagulation/platelet function. One would expect the degree of hypotension to be less in patients receiving TP.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Every 50 patients, the data will be reviewed for quality assurance.

13.2 Quality control/assurance will be performed on CRFs, accountability records (for both EMS organizations and the blood bank), specimen tracking logs, and regulatory records.

13.3 The study coordinator, in combination with the PI, will be responsible for addressing quality assurance and control issues.

13.4 The study coordinator will be responsible for ensuring training documentation logs are complete.

13.5 The blood bank SOPs (see Appendix B) will be referred to for information regarding quality control and assurance of TP.

13.5.1 Quality Control of Blood Products

Regulatory requirements state thawed plasma must remain between 1 and 10°C during transport. Transport containers must be validated to determine if performance meets criteria specified by the manufacturer and regulatory agencies. Temperature data loggers provide a continuous monitor, and an audible alarm when internal temperature exceeds setpoints. A mechanism to indicate unacceptable temperature fluctuations of a product handled outside of the cooler is important for determining product efficacy and patient safety.

The review of quality control worksheets ensures that all work performed is in an approved and reproducible fashion according to TM processes and procedures.

1. The calibration of thermometers used for testing is checked periodically.
2. Quality Control records are reviewed by the QC Senior or designee after work is complete and corrective action is initiated for unacceptable results

13.5.2 See APPENDIX B for Complete Blood Product Quality Control SOP.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.2 Informed Consent Process

14.2.1 Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee (likely a study coordinator) will explain the research study to the subject or LAR and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

14.2.2 Once the patient has reached VCUMC and has been entered into the VCUMC health Care system, efforts will be made by the study coordinator to provide a full explanation of the trial to the patient or LAR/next of kin and to obtain informed consent to continue the trial (see IND Appendix 2, Informed Consent Document). The study coordinator will present the information and seek consent in English or Spanish. The Spanish consent form will be provided and informational and interpretational phase will be presented via the hospital's Language Line (a dial-up translation service) (see IND Appendix 2 Informed Consent Spanish Version). The treating healthcare team will advise the SC whether or not a subject is able to consent.

14.2.3 LARs will be defined in accordance with VCU's IRB Written Policies and Procedures (Section 9, A2).

14.2.4 The consent process will be documented in the clinical or research record.

14.3 Exclusion of Special Populations

Individuals of any gender or racial/ethnic group may participate in this study. Children, pregnant women, and prisoners are excluded due to ethical concerns.

14.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects. The study protocol, documentation, data, and all other information generated will be held in strict confidence.

14.5 Future Use of Stored Specimens and Other Identifiable Data

There will be no stored specimens or data for future use; data will only be retained for according to section 15.4 in this document.

15 DATA HANDLING AND RECORD KEEPING

We will keep paper-based records in secure locked cabinets in the Blood Bank/Transfusion Medicine, and in Trauma Surgery and or the PI's offices. Case report forms will be in locked cabinets in a secure (restricted access/few keys) suite of offices for the PI/study coordinator of the PI. Electronic records will be essentially hospital records of which we will query for vital signs, and other clinical data. Any electronic records that are created will be kept on computers that are behind locked doors and data will be password protected and encrypted. Any data examined by the DSMB or the adjudicator will be de-identified. Any data used for reports the Army or for publication in medical publications will be de-identified.

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the SC, who will ensure that they are accurate and complete.

15.2 Data Capture Methods

Data will be recorded on paper forms, using REDCap online data management software, and centralized to a single electronic database.

15.3 Types of Data

Safety data, clinical data, laboratory data, and data from pre-hospital "run reports" will be examined. This includes demographic data, details of the call during which the patient was enrolled, whether the patient developed any infections during their hospital stay, whether the patient developed multi-system organ failure, types of treatments received in-hospital (blood products, major surgeries, emergency bedside procedures), and concomitant medications.

15.3.1 Concomitant Medications

- Per FDA guidelines, concomitant medications must be kept on record, along with the source/method of information collection (FDA Guidance for Industry: Section IIIB). This information must be collected and stored regardless of the intent to use in data analysis.
- Concomitant medication information collection for PUPTH subjects will begin with any medication and/or medical history that are obtained by EMS in the field or by medical staff after the arrival of the patient to the hospital. The source of this information will be the patient's EMR, family, or the patient him/herself.

Concomitant medication information will continue to be collected for the primary study period.

- Any significant adverse event as defined in the study protocol will warrant collection of concomitant medication data from the EMR.
- Concomitant medications outside of the primary study period will be available to FDA and University auditors via the subject's EMR, which will have comprehensive medication data for the length of the patient's hospital stay.
- Concomitant medication records for each subject will be stored in the regulatory binder for the duration of the study and after study closing in compliance with FDA regulations.
- Concomitant medications will be collected from the EMR and de-identified using only the subject number for the purpose of regulatory compliance.

15.4 Schedule and Content of Reports

The US Army Materiel Command will receive quarterly reports in accordance with grant conditions.

15.5 Study Records Retention

Study records will be maintained for at least three years from the date that the grant financial reports are submitted to the DoD. Study documents should be retained for a minimum of 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations.

15.6 Protocol Deviations

Any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements will warrant a report to the appropriate supervisor as well as to the IRB as soon as possible.
These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

16 REGULATORY DOCUMENTATION

16.1 Each version of the protocol is stored on the shared study drive and in VCU IRB records.

16.2 CVs for VCU study personnel are stored by each employee's department and can be accessed electronically.

16.3 IRB documentation will be stored in the study coordinator's office in a designated binder. If IRB documentation is electronic, it will be stored in the VCU IRB software, RAMS-IRB and can be accessed on demand.

17 PUBLICATION/DATA SHARING POLICY

17.1 Authors on resulting publications will have made significant intellectual contributions to the design and conduct of this study.

17.2 The trial protocol and results will be published in peer-reviewed journals.

17.3 The results of the trial will be reported first to trial collaborators.

17.4 All publications will follow the Consolidated Standards for Reporting Trials (CONSORT) statement.

17.5 The PUPTH Trial will be registered and maintained in ClinicalTrials.gov.

17.5.1 The results of the PUPTH Trial will be reported on ClinicalTrials.gov.

17.5.1.1 Links to published data will be provided through the ClinicalTrials.gov website.

17.6 The PUPTH study protocol will be submitted to Trials for peer review.

17.7 This study must give credit to The Virginia Commonwealth University Center for Clinical and Translational Research (CCTR) and VCU Technology Services in each publication, cited as:

The project [publication] described was supported by CTSA award No. UL1TR000058 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

17.8 Frances Dumenci and Eric Peterson will be cited as having provided us with substantial assistance with advertising and database construction via REDCap.

17.9 Beth Broering, RN, VCUMC Trauma Program Manager will be cited as having assisted us by providing data from the trauma registry that we used to compare and evaluate Plasma Study enrollment data to overall trauma admissions

17.10 Dissemination of results to patients will take place via the media, relevant patient organizations, and the trial website (*http://www.cctr.vcu.edu/news/feature/plasma.html*).

17.11 Emily D. Cochran, RN, CCRN will be cited for her contributions to the study coordinator and trial SOP's.

18 LITERATURE REFERENCES

18.1 Background/Rationale References

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APPENDICES

18.2 LIST OF APPENDED MATERIALS

A. PUPTH Organizational Graphics

B. Blood Bank SOPs

C. EMS SOPs

D. MCV Transfer Center SOP

E. VECTOR SOP

F. Telephone Script for Follow-Up

G. CRFs

i. Adverse Events

ii. Coagulation Labs

iii. Concomitant Medications

iv. Consent

v. Demographics

vi. Disposition

vii. ED Arrival/Departure

viii. EMS

ix. Infections

x. In-hospital Treatments

xi. IV Fluids

xii. Medical History

xiii. Medication History

xiv. Mult-System Organ Failure

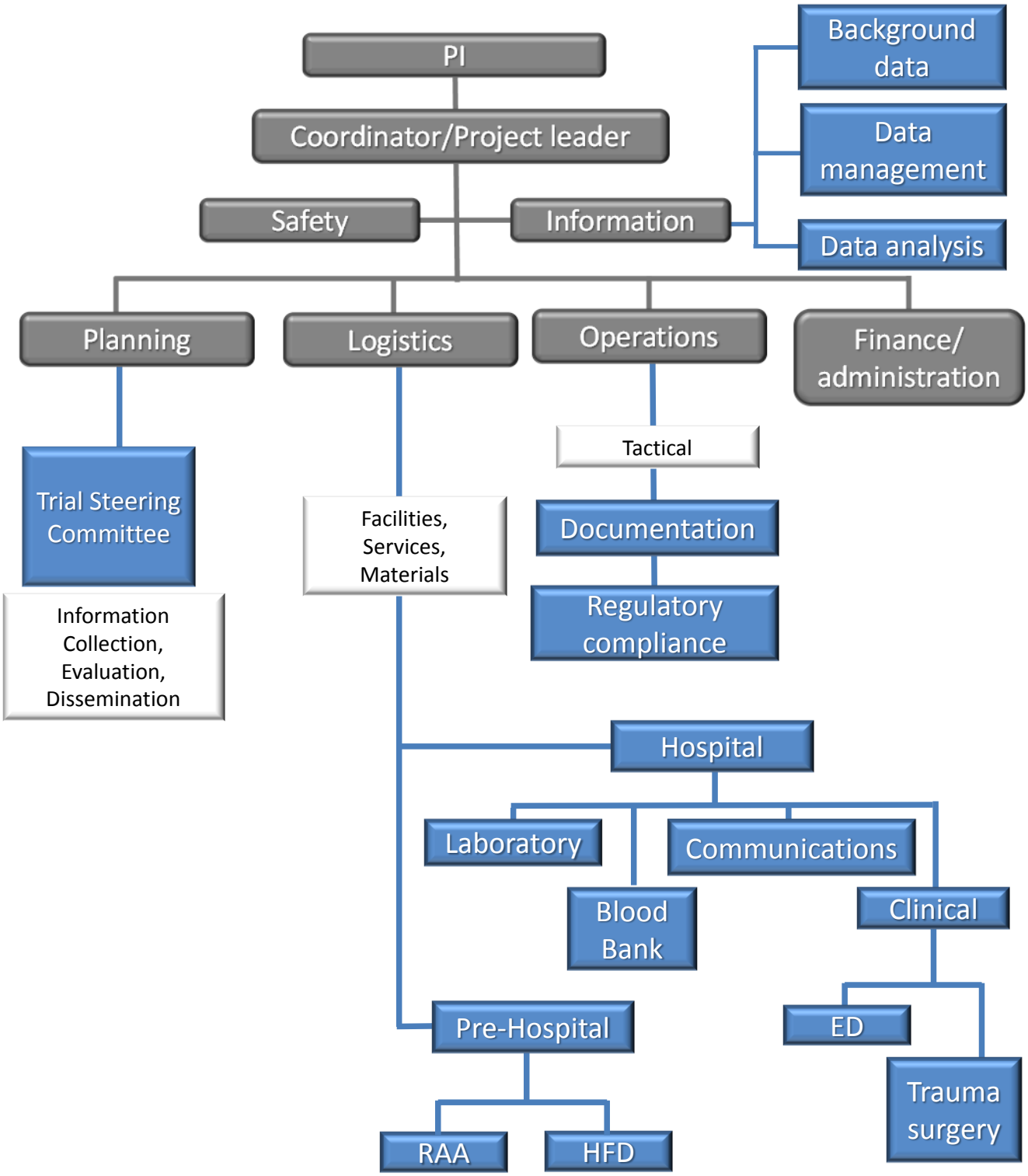
xv. SOFA Score

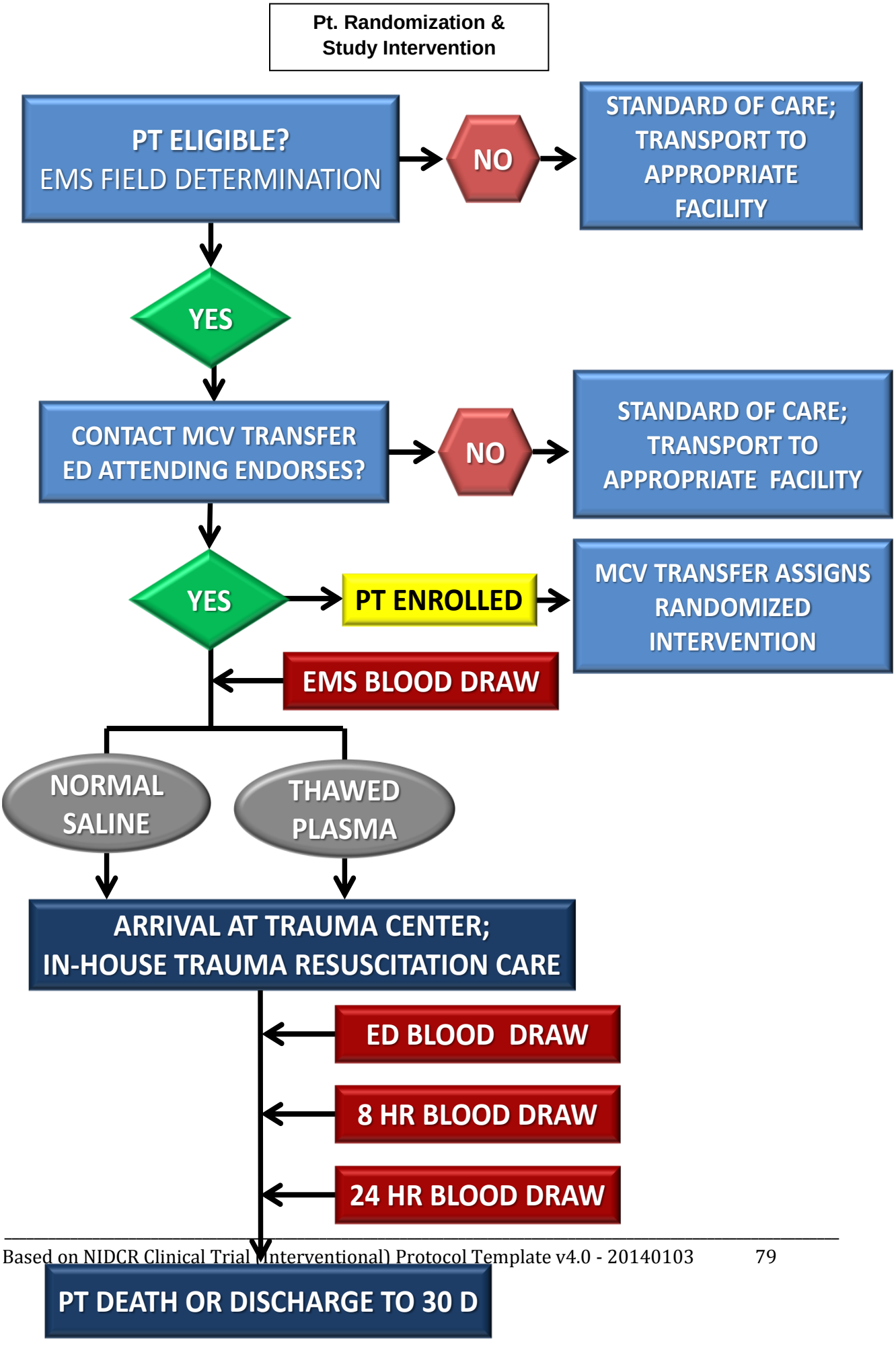
xvi. Toxicology Panel

H. Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Regulatory Requirements ORP Human Research Protection Office (HRPO) Version: 15

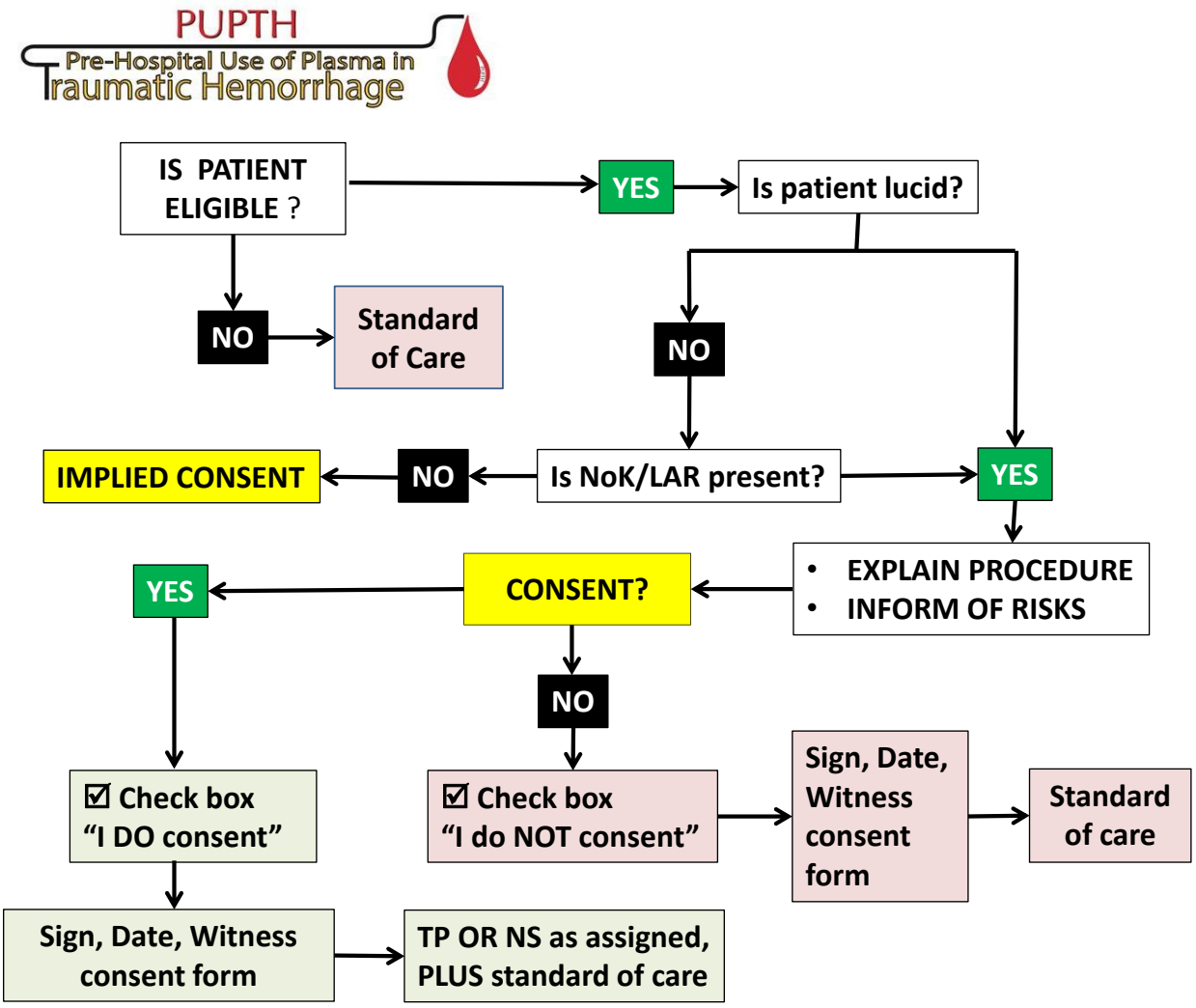
APPENDIX A: PUPTH Trial Graphics

Organizational Flow Chart

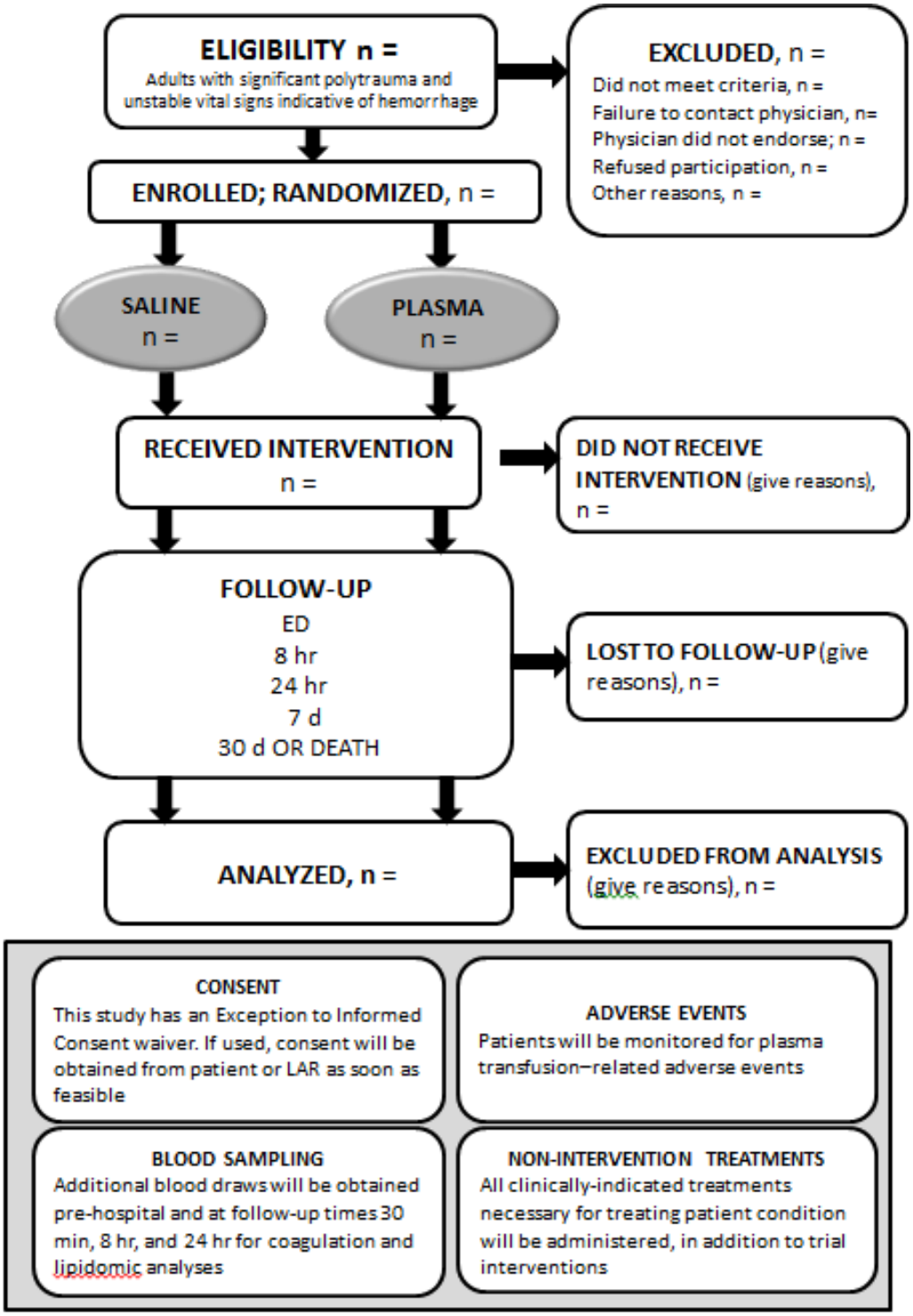



Pt. Randomization & Study Intervention
PT ELIGIBLE? EMS FIELD DETERMINATION
NO
STANDARD OF CARE; TRANSPORT TO APPROPRIATE FACILITY
YES
CONTACT MCV TRANSFER ED ATTENDING ENDORSES?
NO
STANDARD OF CARE; TRANSPORT TO APPROPRIATE FACILITY
YES
PT ENROLLED
MCV TRANSFER ASSIGNS RANDOMIZED INTERVENTION
EMS BLOOD DRAW
NORMAL SALINE
THAWED PLASMA
ARRIVAL AT TRAUMA CENTER; IN-HOUSE TRAUMA RESUSCITATION CARE
ED BLOOD DRAW
8 HR BLOOD DRAW
24 HR BLOOD DRAW
PT DEATH OR DISCHARGE TO 30 D

PUPTH EMS TRIAL FLOW GRAPHIC



PUPTH TRIAL/SUBJECT GRAPHIC FOR TRIAL EVALUATION AND FOLLOW-UP



APPENDIX B: Blood Bank SOP

TITLE: TRANSFUSION MEDICINE PUPTH STUDY PROTOCOL
PURPOSE: To outline the steps for testing, assigning, issuing and returning PUPTH study plasma in Transfusion Medicine.

PRINCIPLE:
The PUPTH Study (Pre-hospital Utilization of Plasma for Traumatic Hemorrhage) is a multi-site Department of Defense sponsored research project. Two units of thawed A positive plasma are carried in electric blood coolers by one supervisor for Richmond Ambulance Authority and one supervisor for Henrico County Fire/EMS. Trauma patients meeting study eligibility will be randomly selected to receive plasma in the field.

The Transfusion Service has a mechanism to verify acceptability of plasma prior to issue and assignment to study patients. Records are maintained to capture all successive steps in the processing, storage, and distribution of blood products. Unused plasma is returned daily to Transfusion Medicine by the EMS supervisors. Returned units are evaluated for specific criteria, including bag integrity, temperature indicator status and data logger temperatures. If found acceptable, the units are returned to the general plasma inventory for reissue within VCU Medical Center. If unacceptable, plasma units are destroyed.

NOTES:
1. ShockWatch blood temperature indicators should be stored at room temperature and must be above 10°C before attaching to plasma units.
2. Plasma must be cold (between 1-10°C) before attaching the ShockWatch blood temperature indicators.
3. The refrigerated coolers should be plugged into an electrical outlet at all times when located in Transfusion Medicine.
4. A stock of frozen A positive plasma with low titers of Anti-B is maintained for the study. A minimum of four study plasma units are thawed, assigned and maintained in the release area refrigerator at all times.

MATERIALS/EQUIPMENT:
Refer to the Master Materials List

PROCEDURE:

A.00 SELECTION AND TESTING OF PLASMA FOR STUDY

A1.00 Selection
A supply of 20 frozen units of type A plasma with low anti-B titers is stocked separate from general plasma in a freezer shelf assigned for the study.
Select enough units to titer from either general stock or incoming inventory to meet the minimum number of study plasma stock.
Avoid lower volume, divided units.
Select units with a segment available for testing.
Remove segment and place in a tube labeled with the unit number. Keep unit frozen during testing.

A2.00 Titering
Open Excel spreadsheet for PUPTH Study Titer Testing. Select worksheet for current week. Place cursor on next open box for unit # and barcode in the unit.

For each unit, make a 1:100 dilution from a thawed plasma segment by adding 10 microliters of plasma to 990 microliters of saline in a labeled test tube.
Place 2 drops of each dilute plasma in a labeled test tube. Add one drop of commercially prepared B cells.
Mix contents and spin at proper time for saline phase in a calibrated centrifuge.
Examine button macroscopically for agglutination.
Interpretation:

No agglutination: titer is below cutoff and unit is acceptable for study
Any agglutination: titer is > 1:100 and unit cannot be used for study.

Record results in appropriate box on Excel spreadsheet and SAVE.
In Product History Review, for each unit acceptable for study, add comment on the unit "anti-B titer < 1:100".
For units unacceptable for study, add comment "anti-B titer >100".
Place study plasma on the freezer shelf designated for PUPTH Study. Units unacceptable for study go into general inventory.

B.00 STORAGE AND HANDLING OF PUPTH PLASMA

B1.00 General Guidelines

A total of four units of plasma are thawed and available at all times for PUPTH. Two units are assigned and tagged for each ambulance service and placed in their respective boxes in the RA refrigerator.
Use tagged units first whether for daily exchange or replacement.
All plasma returned by EMS which meet acceptance criteria must be placed into general stock for use. Do not place units back into PUPTH study stock.

B2.00 Assigning Emergency Release Plasma

Retrieve two thawed units of A positive, low titered plasma to be assigned.
NOTE: Confirm titer is recorded in Product History comment of each unit.
Using the Dispense/Assign application, manually assign the units to patient "BB,EI Stock".
Enter the unit numbers, one at a time, click SAVE.
When warning box pops up, select YES. Select reason as "PUPTH STUDY" from drop down box as assign reason.
Bag tags will automatically print on default printer.
Attach bag tags and FDA Alert Notice to their corresponding units.
Request that another technologist perform a bag tag check utilizing verbal read back.
Each tech will take a turn reading the information to the other tech who is actively listening in order to verify the shared information, and then the roles are reversed to again verify the same information.
Check unit donor number
Check unit product type
Check ABO/Rh of product
Check unit expiration/time

Verifying tech initials the top right of the bag tag if no discrepancies are found.
Place units in the RA refrigerator assigned to the respective ambulance services.

B3.00 DISPENSE OF PLASMA FOR PUPTH STUDY

B3.10 Daily Exchange with Cooler

Retrieve two (2) units of pre-tagged plasma to be dispensed and a cooler.
Using the Dispense application, click on the <ellipsis> button and enter the patient BB, EI STOCK.
Enter the unit numbers of the plasma units to be dispensed.
When exception box pops up, override exception using "PUPTH Emergency Stock" as REASON.
Click SAVE when all units have been entered.
Enter Reason: "PUPTH STUDY". Press TAB to get to COURIER: Enter in the cooler number dispensed. Press TAB to get to appropriate Location: Henrico Ambulance or Richmond Ambulance. Press TAB again. The Device: field will default to PUPTH Storage as appropriate.
Click OK to dispense.
Continue to Attaching Indicators below.

B3.20 ATTACHING BLOOD TEMPERATURE INDICATORS

Prior to attaching the indicator, the plasma units must be between 1-10°C.
Verify the indicators have been stored at room temperature.
Verify the indicator arming window is yellow and the breach window is white.

Firmly squeeze the blister located on the top of the indicator. Verify the arming window changed color from yellow to green, otherwise squeeze the blister again.

Once the arming window is green, remove the indicator from the adhesive liner.
Adhere the indicator to the back of the plasma unit and apply constant pressure for 3-5 seconds to ensure adhesion.
Repeat the process for each plasma unit being dispensed.

B3.30 DISPENSING REFRIGERATED COOLERS

Document the cooler number for each location on the PUPTH1 Form 1.00 Cooler Forms.
Remove the center copies of the plasma bag tags and retain in blood bank.
Place two plasma into each refrigerated cooler, one cooler for Richmond and one cooler for Henrico. The data loggers are already attached to the coolers.
Ask the EMS supervisor or designated study personnel picking up the cooler to write their name on the PUPTH Cooler forms.

Staple the PUPTH Cooler forms to copies of the bag tags for each group of plasma, one for Richmond and one for Henrico and file in the PUPTH study basket.

B3.40 Unscheduled Plasma Dispense

EMS Supervisors are instructed to call blood bank prior to picking up plasma.
Ambulance supervisors should return the yellow copy of bag tags of transfused plasma to blood bank in order to receive replacement units.
Fresh plasma units are dispensed to EMS supervisor in a plastic bag without a cooler.
Follow same steps as Daily Exchange B3.00 but omit entering cooler number as the COURIER.

C.00 RETURN of YELLOW SLIPS

Transfused plasma must be dispensed in Cerner to study patients in a manner similar to emergency release uncrossmatched red blood cells.
Each bag tag should be labeled with the recipient's name and medical record number (trauma name/ MRN) at the patient's bedside prior to leaving ED. The top copy of bag tag is retained by ED for the patient's chart. Yellow copies are returned to blood bank. Follow C.00 for processing yellow sheets.

C1.00 Return the Unit into Inventory

Return the unit into inventory using Return Products application. Select the return Reason "PUPTH-Stock Return".

C1.01 Release Assignment of Unit(s) from BB, EI Stock
The Product Release/Quarantine window will open.
Click in the box to Release Assignment and Select the Reason: "Return-PUPTH Stock".
Enter "N/A" in the Temperature section.
Click OK; click SAVE .

C1.02 Dispense the Transfused Unit to Recipient

Launch the "Dispense and Assign Products" application. NOTE: Do not use the Emergency Dispense task within the "Dispense and Assign"
application.
Dispense the unit to the patient using time and date written on the bag tag by EMS.
A message box opens warning that the product requires a crossmatch. Choose YES to override. Select the Reason: "PUPTH. Stock"
Use "PUPTH Henrico" or "PUPTH Richmond" for the issue location.

C1.03 CREDIT CHARGES FOR TRANSFUSED PLASMA

**IMPORTANT: Study plasma is paid for by the study and therefore must not be charged to any patient account. Use charge viewer to credit patient's account for any transfused study plasma.

D.00 Returned Products

Plasma returned before the unit expiration date and time may be returned to general inventory as long as acceptance criteria are met. Launch Return Products application and use the Reason "Return- PUPTH Stock". Refer to RA406, *Return of Blood and Blood Products.*

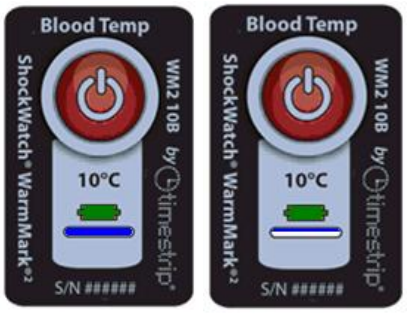
Acceptance Criteria for Returned PUPTH Study Plasma

Temperature of unit with the infrared thermometer is 1-10°C ,
ShockWatch indicator breach window is completely white.
Temperature data from the data logger is all within 1-10°C.
Unit appears normal- ports intact, not leaking, label attached and legible.

NOTE: If the return process cannot be started immediately, document the unit temperature using the infrared thermometer and time the units are returned on the bag tag. Place the units in the release area refrigerator on an empty shelf – not back into stock. Do not return the cooler to the back bench until temperature data is downloaded. When time is available, perform the full process including returning products in Cerner.

D1.00 UNIT TEMPERATURE
Time stamp the bag tag on the plasma.
Upon return of thawed plasma to TM, immediately use infrared thermometer to take the blood product temperature.
Document the temperature on the bag tag.
Check the blood temperature indicator and verify that no part of the breach window has any blue in it. If there is any part of the breach window that is blue, the plasma is not acceptable for reissue and must be wasted.

UNACCEPTABLE:



D2.00 VISUAL INSPECTION
Appearance must be normal. (Ensure integrity of the unit has not been compromised. The unit label must be attached and legible. The container closure must not be disturbed.)
Expiration date must be valid.

D3.00 DOWNLOADING TEMPERATURE DATA FROM DATA LOGGERS

Use the laptop computer with the Dicksonware Secure Software installed on it. Sign on using user name "PUPTH" and password "PUPTH". Connect the data logger to the computer using the provided USB cord.
Double click on the Dicksonware Secure icon on the desktop.
Enter your username and password.
Click on the Download button in the top menu bar of the window. Data will now be downloaded.
When the download is complete a graph appears on the screen.
Click on the tab that says Table on the left top of the screen. Review the data points to make sure all temperatures are within 1-10°C.
If all data points are within 1-10°C, then the plasma is acceptable for reissue.
If two or more data points are not within 1-10°C, then the plasma is not acceptable for reissue.
Click on the SAVE button in the top menu bar of the window.
Select the "Downloaded Data-Table and Graph" option and click OK.
Save the file in the folder named "PUPTH Study Temperature Data". The file name will automatically be created to include the download date. Add to the end of the file name the cooler number associated with the data logger. Also add initials of tech reviewing the data. Example: "Downloaded Data – Tuesday June 17, 2014 cooler 4 BLR".
After saving the data, the next prompt will ask if you want to clear the logger and restart it. Select YES and click OK. Do not disconnect the data logger until the window on the screen closes indicating the logger has been cleared and restarted.
Exit the software program.
Open the "PUPTH Study Temperature Data" folder on the desktop.
Open the IronKey icon on the desktop.
Drag the data logger files you just saved to the IronKey folder.
Disconnect the USB cord from the data logger.
Return the cooler to the back bench near Special Studies and plug into the electrical cord.

D4.00 RELEASE ASSIGNMENT OF UNIT(S) FROM PUPTH -STOCK

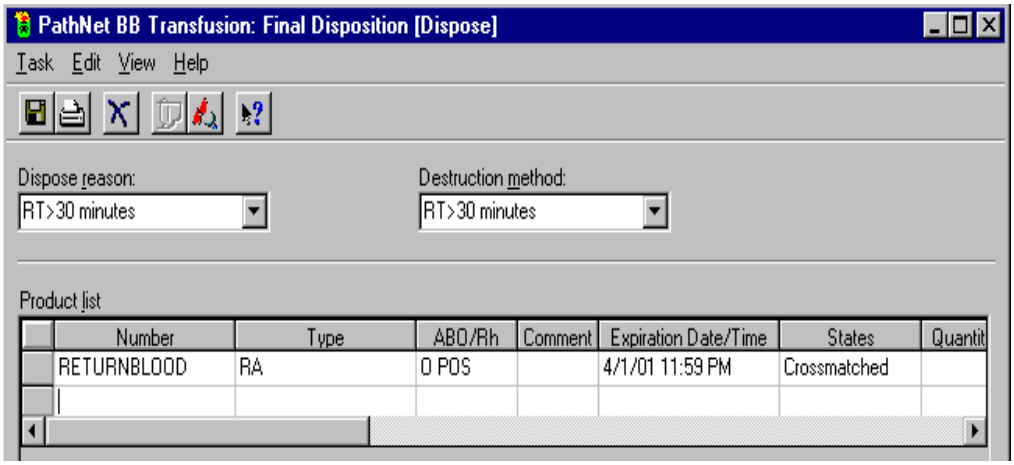
In the Return Product application, the Product Release/Quarantine window opens once the unit number is scanned.
For products accepted for re-issue:
a. Click the box to Release Assignment and Select the Reason: "Return-PUPTH Stock".
b. In the temperature section, enter the following information:
color of the temperature indicator,
data logger temp review,
temperature of the blood product
(e.g. white, data logger temps ok, 5.2°C)

c. Click OK; click SAVE .

d. Remove bag tag and place top copy in the PUPTH Study basket.
3. For units that DO NOT meet the acceptance criteria:
a. Place the product in quarantine. Quarantine is a temporary status; units must be disposed in Cerner using Final Disposition application- see C5.00.
b. Select Quarantine Product under ACTION TO TAKE and select the Reason from the drop down menu. Add comments in the Temperature section same as above (e.g. blue, data logger ok, 12.0°C)

D5.00 FINAL DISPOSE UNACCEPTABLE UNITS

Perform final disposition in LIS for units that are not acceptable for re-issue (wasted).
Make sure a comment was added to unit demographics for unit temp, indicator and data logger status prior to disposal.
Launch Final Disposition application. Make sure disposition mode is [Dispose] . Enter the Dispose reason: "WA- Stored improperly" and Destruction method: "Wasted."
Enter the donor number of the unit to be disposed under Product list: Number. Press ENTER.



The spreadsheet populates with the unit information. Confirm information is correct and SAVE.
Write "wasted" on the bag tag and place the top copy in the PUPTH Study basket..
Write "wasted" on the product label and place on the quarantine shelf. These units are used for Research by Molecular Diagnostic and other departments.

QUALITY CONTROL
The review of daily and weekly reports ensures that all work performed is in an approved and reproducible fashion and that inventory can be reconciled according to TM processes and procedures.
Temperature records of the device (data loggers) will be reviewed by a Transfusion Medicine staff member at designated intervals when unused plasma is returned to the laboratory. Returned plasma will be placed in quarantine until review of the temperature records has been completed.
Dispense and return records of study plasma will be reviewed weekly by the QC Senior or designee, logged electronically on PUPTH1 Form 2.00 and filed in the PUPTH Study Binder.

RECORDS
Refer to QA100, *Record Management*, Table 1.

LIST OF APPENDED MATERIALS
Appendix 1 PUPTH1 Form 1.00 Cooler Sign-Out form
Appendix 2 PUPTH1 Form 2.00 Log Sheet

REFERENCED PROCEDURES:
RA406, *Return of Blood and Blood Products*

REFERENCES:
AABB Technical Manual, 18th edition, 2014, p.213-228.

PROCEDURE RECORD: ASSIGNING, ISSUING, and RETURNING PUPTH STUDY PLASMA

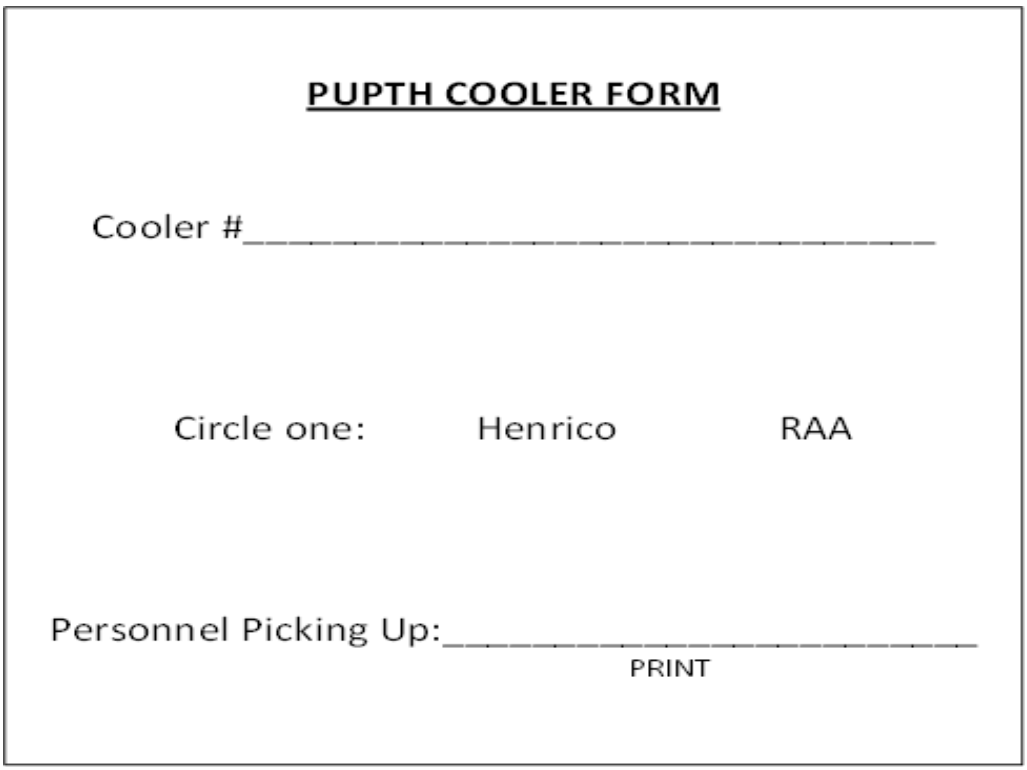
Revised Date	Summary of Changes	Revised By
No previous.	New procedure.	Rashid Bhavnagri Joan Shemenski Brenda Rose

Distributed to:

☐ Main Lab ☐ OR Stat Lab ☐ Apheresis ☐ P:/CP/Blood Bank/Procedures

Approved by:	Date:	Version #: 1
Approved by:	Date:	
Approved by:	Date:	
Approved by:	Date:	
Start Date:		Archive Date:

Appendix 1



TITLE: TRANSFUSION MEDICINE PUPTH STUDY QUALITY CONTROL PROTOCOLS

PURPOSE:

To help ensure that blood products transported in mobile, electric refrigerated coolers are maintained at appropriate temperatures.

PRINCIPLE:

Regulatory requirements state thawed plasma must remain between 1 and 10°C during transport. Transport containers must be validated to determine if performance meets criteria specified by the manufacturer and regulatory agencies. Temperature data loggers provide a continuous monitor, and an audible alarm when internal temperature exceeds setpoints. A mechanism to indicate unacceptable temperature fluctuations of a product handled outside of the cooler is important for determining product efficacy and patient safety.

MATERIALS AND EQUIPMENT:

Refer to the Master Materials List

Documents/Forms:

Quality Control of Refrigerated Coolers
Thermometer Checks
Alarm Checks of Transfusion Medicine Equipment
Blood Temperature Indicator Quality Control

PERFORMANCE PARAMETERS:

Records must indicate transport temperatures of 1-10°C are maintained at all times for refrigerated cooler.
QC and temperature data loggers can accurately monitor temperatures of coolers and alarm when appropriate.

NOTES:

Routine QC of refrigerated coolers is performed semi-annually and includes use of the data loggers.
Temperature data logger alarm check QC is performed quarterly.
Temperature checks of the temperature data loggers are performed monthly.
Temperature data from data loggers are downloaded and reviewed before plasma is placed back into the general inventory. Refer to the procedure *Assigning, Issuing, and Returning PUPTH Study Plasma* for detailed instructions.

5. Quality control on blood temperature indicators is performed upon receipt of new lot numbers. Blood temperature indicators are stored at room temperature.

PROCEDURES:

I. REFRIGERATED COOLER QC

A.00 SET UP FOR QC

Inspect coolers for cracks, punctures or poor closure of the lid. If cooler appears damaged, discontinue use.
For "routine semi-annual QC", select a representative cooler for transport temperature range. Rotate coolers each test period.
Select two units of thawed plasma from the quarantine shelf.
Record the configuration for testing on the Quality Control of Refrigerated Coolers form (e.g. number and component type of units being tested) along with the serial number of the thermometer being used, cooler ID, date, initials, and time started.

B.00 PACKING COOLERS FOR QC

Place two units of thawed plasma into the cooler.
Place a NIST-calibrated thermometer with glycol bottle probe into the cooler. Use the temperature data loggers for monitoring temperature.
Close the cooler lid.
Record time packed on the Quality Control of Refrigerated Coolers form.

C.00 READING/ RECORDING TEMPERATURES FOR QC

Allow the data logger to record temperature for 24 hours.
Once 24 hours has elapsed, record the stop time on the Quality Control of Refrigerated Coolers form.
Using the computer with the Dicksonware Secure Software installed, connect the data logger to the computer via USB cord.
Double click on the Dicksonware Secure icon on the desktop.
Enter your username and password.
Click on the Download button in the top menu bar of the window. Data will download.
When the download is complete, a graph appears on the screen.
Click on the Save button in the top menu bar of the window.

Select the "Downloaded Data-Table and Graph" option and click Ok.
Save the file in the folder on the p drive named "Refrigerated Cooler QC". Name the file according to QC performed and date.
Document the file name on the Quality Control of Refrigerated Coolers form.
After saving the data, the next prompt will ask if you want to clear the logger and restart it. Select yes and click Ok. Do not disconnect the data logger until the window on the screen closes indicating the logger has been cleared and restarted.
Exit the software program.
Disconnect the USB cord from the data logger.

D.00 INTERPRETATION OF RESULTS/CORRECTIVE ACTION

If the temperature of the cooler falls outside of acceptable ranges (1- 10°C for transport) during the 24-hour test period the cooler must be removed from use. Notify the QC senior tech or designee for further investigation.
Acceptable ranges for other packing configurations are defined following validation results.

II. TEMPERATURE DATA LOGGER QC

A.00 THERMOMETER

Refer to QC21 *Thermometer Calibration Checks* for detailed instructions.

B.00 LOW ALARM FUNCTION

Prepare a container of ice, salt, and water to achieve a solution with a temperature approximately -4°C.
Place the glycerol probe bottle from the data logger into the -4°C solution along with the NIST calibrated thermometer.
Allow the bottle to remain in the solution, with periodic gentle agitation, until the data logger's alarm activates.
Record the temperature on the data logger and the NIST standard reading at alarm on the Alarm Checks of Transfusion Medicine Equipment form.
Remove the glycerol bottle from the solution and allow to return to normal temperature.

C.00 HIGH ALARM FUNCTION

Prepare a container of ice and water to achieve a solution with a temperature approximately 16-20°C.
Place the glycerol probe bottle from the data logger into the 16-20°C solution along with NIST calibrated thermometer.
Allow the bottle to remain in the solution, with periodic gentle agitation, until the data logger's alarm activates.
Record the temperature on the data logger and the NIST standard reading at alarm on the Alarm Checks of Transfusion Medicine Equipment form.
Remove the glycerol bottle from the solution and allow to return to normal temperature

III. BLOOD TEMPERATURE INDICATORS

A.00 RECEIPT

When a new lot number of blood temperature indicators are received, enter the information on the Reagent Inventory Receipt Log (electronic form) refer to QC2, *Receipt of Incoming Reagents*).

Verify accuracy of the quality assurance document (Certificate of Conformance). Record initials and date; place the QA document in the QC Senior's mailbox as notification that the indicators have arrived. The QC document is filed by the QC Senior in the Blood Temperature Indicators Notebook in the QC Senior's office. Place the boxes at room temp on the supplies shelf with red "Do Not Use this Lot Number" stickers until visual inspection and QC has been performed on the lot.

B.00 LOT QC

1. Perform a visual inspection:
The arming window on the indicator should be yellow.
The breach window on the indicator should be white.
2. If the visual inspection passes, go on to check the indicator performance:
Prior to testing the new lot of indicators, the blood products must be between 1-10°C. Pull two wasted plasma units from the quarantine shelf.
Verify that the indicator arming window is yellow and the breach window is white.
Firmly squeeze the blister located on the top of the indicator. Verify the arming window changed color from yellow to green, otherwise squeeze the blister again.
Once the arming window is green, remove the indicator from the adhesive liner.
Adhere one indicator to each back of the wasted blood products. Apply constant pressure for 3-5 seconds to ensure adhesion.
Place one unit into a refrigerator and leave the other one on the counter at room temperature.
After 20 minutes, check the breach window of each indicator.
Acceptable QC is considered:
Refrigerated unit: breach window should be white.
Room temperature: breach window should have at least some portion appear blue. The window does not have to be completely blue.
Record results on the Blood Temperature Indicator Quality Control form.
If QC fails or any discrepancies are noted during the process, quarantine the lot and contact the QC Senior or MTIC.
If QC is acceptable, place a green sticker "This Lot is Ready for Use" on the box and move to the supplies shelf in the laboratory.

IV. EVALUATING RESULTS OF STORAGE TEMPERATURE MONITORING

The Transfusion Medicine staff member will review forms for completeness.
If results are in range (1-10°C for transporting refrigerated products), the coolers are acceptable for transporting plasma for transfusion.
If results were not in range, perform Root Cause Analysis and Corrective Action. Involve PUPTH study and ambulance personnel, TM QA Coordinator, TM Manager, and Medical Director.

QUALITY CONTROL

The review of quality control worksheets ensures that all work performed is in an approved and reproducible fashion according to TM processes and procedures.
The calibration of thermometers used for testing is checked periodically.
Quality Control records are reviewed by the QC Senior or designee after work is complete and corrective action is initiated for unacceptable results.

RECORDS

Refer to Table 1, QA100, *Record Management.*

LIST OF APPENDED MATERIALS
Appendix 1 Quality Control of Refrigerated Coolers, PUPTH2 Form 1.00
Appendix 2 Blood Temperature Indicator Quality Control, PUPTH2 Form 2.00

REFERENCED PROCEDURES:
QC21 *Thermometer Calibration Checks*
QC2, *Receipt of Incoming Reagents*

REFERENCES:

AABB Technical Manual, 18th edition, 2014, p.213-228.

AABB Standards for Blood Banks and Transfusion Services, 29th edition, 2014, p.14-15

PROCEDURE RECORD: PUPTH STUDY QUALITY CONTROL PROTOCOLS

Revised Date	Summary of Changes	Revised By
No previous	New Procedure	Joan Shemenski Brenda Rose

Distributed to:
☐ **Main Lab** ☐ **OR Stat Lab** ☐ **Apheresis** ☐ **P:/CP/Blood Bank/Procedures**

DATE: **FEBRUARY 19, 2015**

GROUP: **EMS**

PREPARED BY: P. S. REYNOLDS

APPENDIX C: EMS SOPs

PUPTH
Pre-Hospital Use of Plasma in Traumatic Hemorrhage

EMS PROCEDURAL GUIDELINES

OUTLINE

Objectives: Discuss issues related to:

1. **Protocol activation**
   - Eligibility
   - Procedures
   - Incidentals: Mass casualty, Randomization, Document synchronization

2. **Protocol adherence and risk assessment**
   Document minimum requirements that must be adhered to by prehospital provider agencies involving use of thawed fresh frozen plasma , referred to in this document as FFP
   - inventory
   - maintenance, handling
   - protocol activation
   - infusion
   - patient handoff
   - disposal

3. **Risk assessment platform**
   - Ensuring protocol adherence
   - Adverse events
   - Product contamination
   - Documentation

4. **Briefing/Debriefing**
   - scheduling

PROTOCOL ACTIVATION

Callout procedure

- On-scene Medic in Charge notifies EMS/S for "POTENTIAL VCU PLASMA TRIAL ACTIVATION"
- Notify VCUMC TRANSFER CENTER TO CONTACT ON-CALL STUDY PHYSICIAN for medical direction.
- If non-eligible, EMS/S stands down, Medic in Charge continues with standard of care

Patient eligibility

- Blunt or penetrating trauma
- ≥18 yo
- Hemodynamically unstable: BP systolic ≤ 70 or BP 70-90 with HR ≥ 108
- Major ongoing hemorrhage with unstable VS
- Consent criteria
    - Lucid and does not refuse
    - Unable to give consent, LAR does not refuse
    - Unable to give consent, no LAR available→ Exception from informed consent

Exclusion criteria

- Opt out wristband
- Jehovah's Witness
- Refusal by patient or LAR
- Communication barrier
- Non-salvageable
- DNR documentation
- SCA/CPR prior to randomization
- Penetrating head trauma
- Age < 18
- Known obvious pregnancy
- Prisoner
- Arrival of EMS/S when transport underway
- Inability to obtain IV access
- Burn injury > 2% BSA

PROTOCOL SOP

- EMS supervisor has overall responsibility for coordinating the teams,
- Patient is transferred to ED at the end of the handover
- Plasma is transferred between Blood Bank and EMS, EMS and ED, and/or Blood Bank
- Administer product enroute
- The AIC identifies and hands information, samples over to key receiving people

1. PREPARATION

- Contact **MCV TRANSFER**. Identify as "POTENTIAL VCU PLASMA TRIAL ACTIVATION".
- They will notify Attending Physician on call for Permission to Activate
- If physician gives assent, **MCV TRANSFER consults Randomization schedule** to determine product to be administered (NS or Plasma).

2. IDENTIFICATION/ASSIGNMENT

- Formally identify the patient. Document patient's ID number, surname, first name, and date of birth. (IF KNOWN OR FEASIBLE)
- Open PUPTH-supplied blood draw kit. Attach PUPTH wristband to patient.
- Check product (NS, TP) has been entered on the study record/patient run sheet to ensure correct protocol-assigned product is given.

3. CONSENT

- ***If feasible***, explain the procedure to the patient/NoK. Give information to the patient/NoK about the potential side effects of transfusion.
- ***If feasible***, obtain consent from the patient/NoK for the transfusion to take place.
- ***OTHERWISE*** → **PROCEDURE FOR IMPLIED CONSENT**
- Check "I do" vs. "I do not" consent.
- Consent form includes options
    - **"I do consent"**
    - **"I do not consent"** (Jehovah's Witnesses);
    - **"Implied consent"** (patient unable to give consent, NoK not available on scene)
- Document consent option in patient run sheet
- Obtain witness signatures to consent.

4. CANNULATION/PERIPHERAL VENOUS ACCESS

- Cannulate the patient according to standard operating procedures for trauma.
- Establish at least one, and preferably two, large bore (at least 18 ga, preferably 16 or 14 ga IV. If TP is to be given, line must be dedicated
- Ensure cannula is patent.
- Assess the need to flush the cannula prior to transfusion and following procedure.
- Secure with non-allergenic tape or IV dressing
- Ensure cannula is well secured.

If plasma is to be administered:

- ***Other drugs should not be added to plasma or plasma line.***
- *Do NOT prime transfusion sets with normal saline 0.9%. Do NOT flush plasma sets post-transfusion with normal saline 0.9%.*

If saline is to be administered:

- Saline is administered per ODEMSA protocol, IV or IO administration

FOR ALL ENROLLED PATIENTS:

Ensure that the patient meets eligibility criteria for protocol inclusion.

5. BASELINE OBSERVATIONS

- Obtain patient VS [pulse (ECG), respiratory rate, oxygen saturation, blood pressure, and temperature] prior to beginning transfusion (standard of care monitoring).
- Document VS on patient run chart and/or specific protocol transfusion record.
    - Continue to monitor every 5 min per ODEMSA protocol.

6. PRE-INFUSION

- Set up blood component delivery set per BB guidelines
- Inspect protocol TP fluid pack for defects prior to infusion. Particular attention should be paid to package integrity, discoloration, presence of clots
- Confirm protocol fluid type according to randomization schedule

COAGULATION STUDY DATA:

- Blood draw from peripheral vein:
- 4 four vacutainer tubes (one EDTA purple-top 5-mL and 2 citrate blue-top 5-mL, one 5-mL specialized tube from VCURES coagulation laboratory; total volume 20 mL) will be drawn, and transported at room temperature to the ED with the research subject

7. INFUSION

- PLASMA INFUSION RATE: gravity feed with NO external pressure

- [Note: most scene/transport times in the Greater Richmond area < < 30 min. Document how much protocol fluid was given during transport upon arrival at ED. As patients are supposed to receive 2 units plasma, inform ED re how much volume administered enroute]
- For plasma patients, perform visual observation for TRALI (rashes, level of consciousness, and change in VS). For all enrolled patients, monitor temperature, pulse, and blood pressure.
- Document volume and rate of all additional fluids, medications given
- Document product-identifying number, volume transfused, rate of transfusion.

8. TRANSPORT & ED ARRIVAL

- Notify ED triage that patient is enrolled in VCU PLASMA TRIAL
- If transport time is less than 30 min, infusion is continued, and remaining product delivered to ED personnel
- EMS/S returns plasma transport box to Blood Bank for restocking, handoff documentation, tagging?
- Blood samples given to VECTOR runner OR PUPTH dropbox in ED utility room
- COMPLIANCE TRACKING: Deposit compliance card in ED PUPTH dropbox

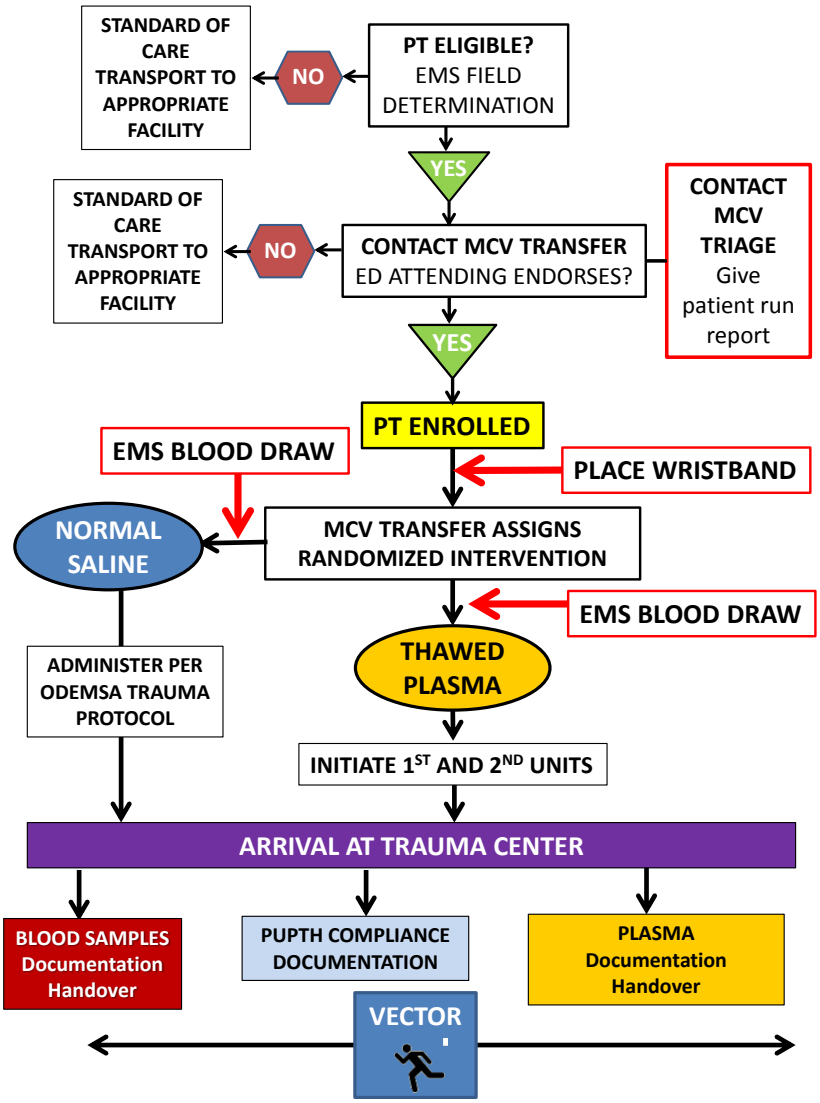
9. COMPLIANCE REVIEW

- **At least once per month or as needed**
- **Review enrolled patients for eligibility, compliance with protocol, blood draw problems, handover problems, documentation**
- **WHO: EMS supervisors, medical director, PUPTH compliance officers, members of PUPTH Trial Steering Committee.**

QUERIES

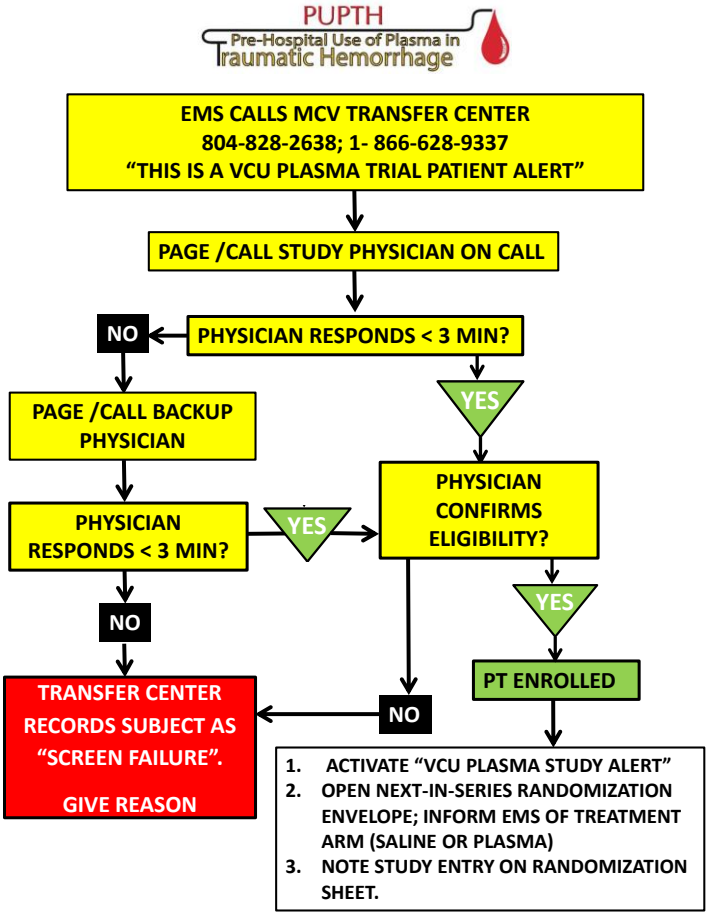
Q: Mass casualty incidents with > 1 critical patient meeting criteria?
ANS: FIRST PT WITH PATENT IV ESTABLISHED

Q: Randomization scheme- how designed, communicated?
ANS: Randomization scheme designed by Biostatistics; sequence in numbered, sealed envelopes. MCV TRANSFER will communicate patient allocation (NO physician involvement).

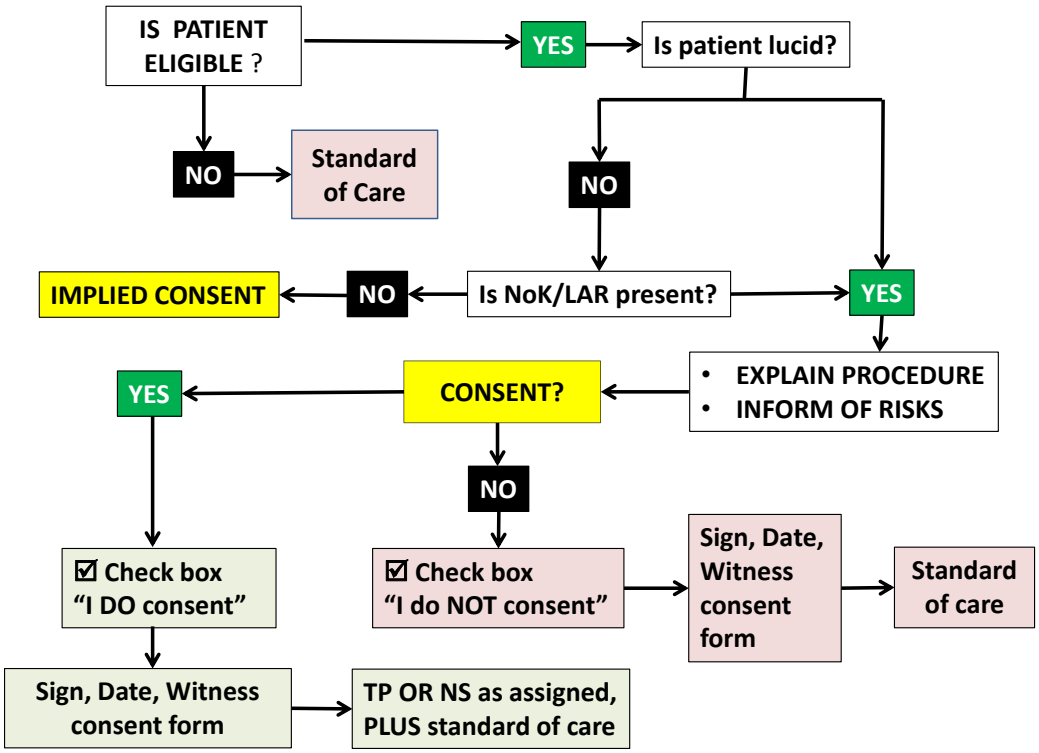


1. EMS TASK FLOW

2. VCU PLASMA TRIAL ACTIVATION: MCV TRANSFER CENTER RESPONSIBILITIES



3. CONSENT



ENSURING ADHERENCE TO PROTOCOL: NEEDS

1 EMS provider adherence to protocol
2 Agency governance system for EMS risk management
3 Identification of agency requirements
4 Oversight for adherence

Designation of EMS individuals qualified to transfuse product (EMS supervisor, ALS PROVIDERS)

- Responsibilities/Requirements
- Standard operating procedures
- Training
- Sign-off training documentation
- Oversight

Briefing/debriefing/oversight management

- EMS Well-established cultures of briefing before every shift
- AGENCY/STUDY COORDINATORS: regular multidisciplinary meeting.

Situation awareness

EMS/S is responsible for situation awareness at handover, and regularly stands back to make safety checks

Training

A high turnover of EMS crews/staff requires

- regular refreshers
- The study protocol and blood product handling protocol can be learnt in 30 min.
- CITI training online
- Online training plus competency quiz
- Documentation for compliance to be sent to VCUMC IRS Compliance officer (E D Cochran)
- Laminated checklists detailing the process provided on each unit

Review meetings

- Regular team meetings to review events.
- Crew to debrief after every protocol-activated call
- SOP clinical governance meetings, where problems and solutions can be openly discussed

RISK ASSESSMENT FRAMEWORK FOR ADVERSE EVENTS

Four main risks:

1. Bacterial contamination *introduced* during maintenance, handling, storage, or thawing;
2. Bacterial contamination **exacerbated** during post-thaw storage;
3. **Coagulation factor activity compromise** as a result of storage conditions (temperature fluctuations, inadequate temperatures);
4. **Transfusion-related adverse reactions:**
    - **Mild allergic**
    - **Moderate to severe allergic**
    - **Acute hemolytic**
    - **TRALI**

GENERAL EMS RESPONSE FOR ALL REACTIONS:

1. **Immediate action**:
    - STOP TRANSFUSION
    - Keep IV open with 0.9% NaCl
- Document vital signs. (BP, HR, RR, temp, other)

2. **Notification**
    - **Notify physician on call for the PUPTH Trial and the ER attending (if different))**
    - **Notify the Blood Bank (**the blood bank will take responsibility for documenting and follow-up of a transfusion reaction and will halt further release of this blood product and pt testing for antibodies etc.

    - **Bruce D Spiess, MD, Principal Investigator 804-828-2267; Telepage: 804-828-0951 and ask to page Dr Spiess**
    - **STICU [Surgical Trauma ICU] attending on call)**
    - **Page the PUPTH Trial Study Coordinator**
3. **Documentation**

    Document decision process in patient run record.

Syndrome	Cause	S/S	TX
Allergic mild	Antibodies to transfused plasma proteins	Pruritis, hives- limited to small area	Administer antihistamines If no improvement in 30 min treat as moderate to severe
Allergic moderate to severe	Antibodies to plasma proteins usually IgE; can be IgA	Temp increases 1.5 deg C within 15 min Generalized hives, bronchospasm and dyspnea, abdominal pain, hypotension, nausea, anaphylaxis	Administer antihistamines, epinephrine, vasopressors and corticosteroids as needed
Acute hemolytic? Issue with plasma?	*Intravascular hemolysis usually due to ABO incompatibility*	*Hemoglobinemia /uria, fever, chills, anxiety, shock, flank pain, chest pain, unexplained bleeding, cardiac arrest*	*Treat shock with vasopressors; maintain airway; increase renal blood flow; administer fluids*
TRALI	Immune-mediated capillary leak syndrome; possibly accumulation of bioactive lipids	Acute respiratory distress usually within 1 – 2 hours of transfusion. sudden development of dyspnea, severe hypoxemia (O2 saturation <90% in room air), hypotension, fever develops within 6 hours after transfusion usually resolves with supportive care within 48 to 96 hours. Although hypotension is considered one of the important signs in diagnosing TRALI, hypertension can occur in some cases. One of the leading causes of death due to transfusion reported to the FDA.	O2; airway support! IV fluids, vasopressors for blood pressure support
TACO **Transfusion-**	Rapid transfusion of large volumes of blood product	dyspnea, orthopnea,	

associated circulatory overload		peripheral edema, rapid increase of blood pressure	

REFER TO BLOOD BANK SOP

SHIFT CHANGE

Each 24 hr shift change:

- EMS/S picks up new plasma from Blood bank, returns appropriately-labelled unused product
- DOCUMENTATION, LOG
- Check product refrigeration unit on EMS/S vehicle
    - Maintenance logs updated
    - Temperature logs updated

Requirements for the Thawing, Storage, and Labelling of Thawed FFP

- Designated EMS personnel received thawed plasma at **the beginning of every 24 hr shift**
- Once thawed, plasma must either be
    - infused
    - maintained in continuous storage at 2-6°C for up to 24 hours.
- It must be returned to Blood bank every 24 hours

Quality Control Blood Bank SOP

- Perform daily temperature quality control check of storage equipment (or at shift change, every 12 hr/24 hr **) EMS must also inspect shock watch temperatures on refrigeration units as well as temperature indicators on plasma units for compliance with protocol**
- Weekly cleaning storage unit or more frequently if required

Plasma allocation refer to Blood Bank SOP

- time and date of thawing
- time and date of expiration
- labelling of thawed product
  Maintenance
- Place the thawed FFP in the refrigerator (2-6°C) until issue.
- Before infusion product must be inspected for evidence of breakage, clots, fibrin or turbidity at the time of issuing.
- verify patient's eligibility
- document patient and issue details
- Document patient VS (BP, HR, RR, temperature)
- Provide hard copy of report for patient's case notes/run sheet

Storage and handling requirements

- Temperature ranges and units,
- Thawed FFP plasma 2-6^{o}C

Product inspection

- regular: daily / shift change (RECOMMENDATIONS)

BLOOD BANK TO EMS HANDOVER

Removal from Storage

- minimize handling of product outside of refrigerator or freezer so that maximum temperature requirements are not exceeded.
- Product must be maintained in a validated refrigerated transport container until it is to be administered.
- Product must be handled and stored in a way that minimizes the opportunity for product tampering/contamination to occur.
- Prior to providing plasma for transfusion, inspect bag for signs of tampering, leakage, clots, fibrin or turbidity. Look for stored thawed components for clots, fibrin or turbidity. Components with unusual appearance are not acceptable for release or infusion

Return of product to Blood bank if unused

DOCUMENTATION

GOALS

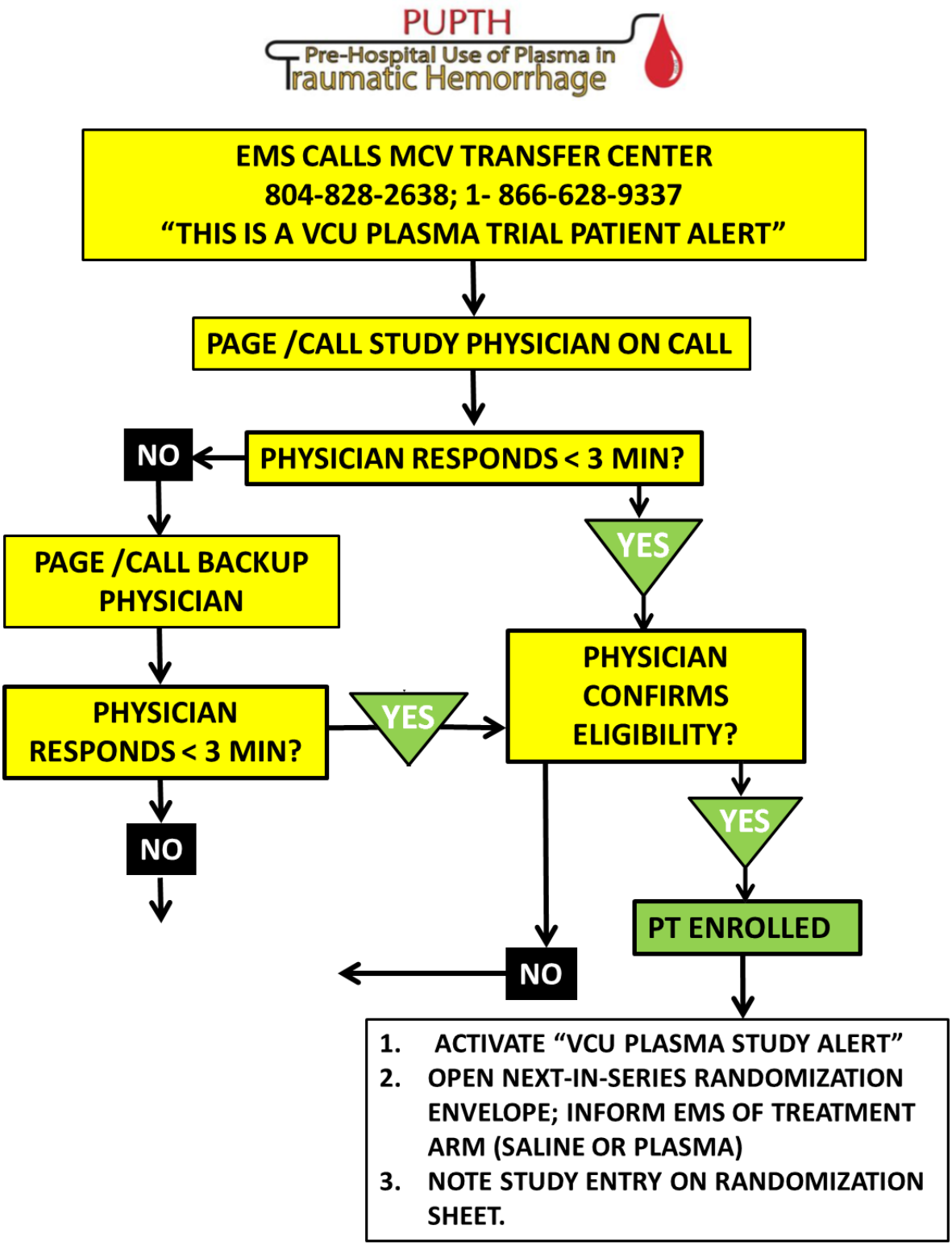
- Records to be kept in such a way so that all steps may be accurately traced.
- Records to be legible, permanent, dated and identification of person responsible for each step.
- A procedure to deal with product loss (splitting/ bursting/contamination of product) must be established.

Inspection of Product Prior to Infusion

- Each product issued for transfusion shall be inspected by staff before release from the laboratory to verify EMS information and integrity of the product container.
- Each product issued for transfusion shall be inspected by EMS before release from the laboratory to verify product information and integrity of the product container.

Approved by:	**Date:**	**Version #: 1**
Approved by:	**Date:**	
Approved by:	**Date:**	
Approved by:	**Date:**	
Start Date:		**Archive Date:**

APPENDIX E: MCV Transfer Center SOP



APPENDIX F: Telephone Script for Follow-Up

Script for Phone Contact to Assess 30 Day Mortality

If the Subject is discharged prior to day 30 following the trauma injury, the study team will attempt to contact the subject on or about day 30 to determine his/her health status.
The patient's discharge information will be available to the interviewer (PI or SC) at the time of this call. If the patient cannot be reached, as described in the "Information and Research Consent to Continued Participation Form" the LAR or NOK may be contacted to determine the subject's status.

Subject: _____ Phone: _____
LAR: _____ Phone: _____
NOK: _____ Phone: _____

Script:
Hello Mr./Mrs. _____ I am (caller's name), the (PI Study Coordinator) for the VCU Plasma Study. (Pronouns will change depending on whether contact is with study subject, LAR or NOK). As part of the Plasma Study, I am calling to find out how (study subject) is doing following (your) injury. Have you had any problems since your injury that required you to see another doctor? Have you been treated in an emergency room since you were discharged or any other hospital since your initial discharge?

Now that completes our call and our study follow-up. Do you have any questions for me? If not, thank you and have a good day.

Information obtained from: _____ (Circle) Subject, LAR, NOK
30-day mortality (Circle): Yes No
Interviewer's Initials: _____
Date: _____
Time: _____

APPENDIX G: CRFs

- Adverse Events – rev9112014
- Coag labs-08042015
- Concomitant medications-30032014
- Consent 04032015
- Demographics rev08022015
- Disposition rev992014
- ED times07042015
- EMS
- Infections04032015
- In Hospital Treatments rev07042015
- IV Fluids 04032015
- Medical History ver08022015
- Medication Historyver08022015
- SOFA 04042015
- Tox panel04042015

Appendix H: PUPTH Protocol for VECTOR Plasma Exchanges

Daily Cooler Exchange

- Every day between 0730 and 0830 (including weekends) the coolers from Richmond Ambulance Authority (RAA) and the Henrico County EMS will be exchanged. This will primarily be done by the VECTOR RA coming off the overnight shift but may entail communication with the RA coming on at 0800 to coordinate both cooler exchanges. Only one cooler can be transported at a time. Therefore, either one RA will make 2 trips or the job will be split between 2 RA's. If there is a trauma during pickup window you can exchange cooler and plasma at same time. Call the Blood Bank (628-7058) for help with planning in this situation.
- EMS will notify VECTOR via the VECTOR pager of arrival and wait outside of back door (facing the White House) of the Gateway Building.
- VECTOR RA will meet EMS supervisor near back door of Gateway.
    - Unplug cooler (light will go off), power cord remains in EMS vehicle.
    - Use bungees to secure cooler onto collapsible hand truck located in EMS truck.
        - Unfold hand trucks and lock by pulling up black latches on sides, putting down bottom and securing hand locks on bottom next to wheels.
        - Wrap bungee cords under and over cooler and attach to hand truck.
    - Deliver cooler to Blood Bank on 6th floor of Gateway Building.
    - Ring doorbell next to Anatomic Pathology Specimen Receiving window.
    - Blood Bank staff will have a replacement cooler with 2 units of plasma ready for you to pick up. Exchange the cooler on the hand truck.
    - Print your name on the PUPTH Study form provided by Blood Bank staff member and indicate which EMS squad the cooler came from/is going to (RAA or Henrico EMS) and the number of the cooler.
    - Take cooler directly back to EMS vehicle and plug back into power source immediately, making sure that light goes back on.
    - Remember to collapse hand truck and place it back in vehicle.

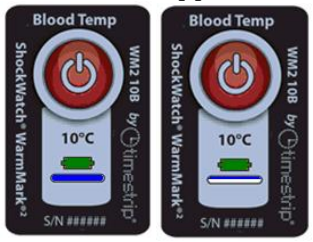
Cooler Information

- While plugged in the coolers keep the plasma at 1-6°C. They are designed to transport at 1-10°C. It is still very important to transport and plug back in as quickly as possible.
- Each cooler has a Data Logger attached to the top via Velcro that logs the temperature of the cooler every 5 minutes per FDA standards. The Blood Bank staff plugs this in to log data every 24 hours. Be careful not to dislodge Data Logger.
- The coolers aren't too heavy; they have handles on both sides and a latch which must be closed during transport. The coolers are designed to be relatively waterproof including the exterior labels. If there are any problems with the coolers or Data Loggers contact the Blood Bank. They expect the coolers to be well traveled and have extras as backup.

Replacement Plasma Pickup

- The plasma bags that have been used on the trauma patient will be discarded in the ED but the yellow form with each bag will be completed by the EMS Supervisor. These need to be returned to the Blood Bank – you may be asked to do this when you go to collect the replacement bags. If you are not asked, ask the EMS Supervisor if they want you to take the yellow form.
- Once the EMS Supervisor's vehicle has arrived at VCU go to the Blood Bank and collect the replacement plasma. Blood Bank is staffed 24/7.
- Ring the doorbell, identify yourself as VECTOR RA, and tell the blood bank tech that you are there to pick up replacement plasma for the squad (RAA or Henrico EMS).
- The blood bank tech will issue you 2 units of replacement plasma in a plastic bag. (Not cooler).
- Sign the form and **write R or H on the bags** indicating which squad the plasma is designated for.
- Upon issue of the plasma the blood bank staff will attach a temperature indicator to the back of each of the 2 plasma units. This is what the indicator looks like upon placement:

If en route the temperature indicator develops **any blue** in the white space as seen below, the plasma **CANNOT be used by EMS**. If this happens return the plasma to the Blood Bank.



- The plasma must be taken directly to the cooler in the EMS supervisor's vehicle to remain at an appropriate temperature. You have approximately 10 minutes before the indicators will turn blue.
- Before placing the plasma in the cooler verify that the temperature indicator window is still white.

Plasma Information

- EMS will only carry 2 units of plasma at a time. That is the maximum that a patient will be given for the purpose of this study. Even if the full 2 units of plasma are not used we still carry on with our protocol as if both units have been depleted.
- Allowing the plasma to exceed 10°C increases the risk of bacteria proliferation which could lead to sepsis if given to a trauma patient. However, if this happens the plasma is still viable for a more stable patient and should be returned to the Blood Bank for alternative use.

- All plasma is type A. It is compatible for all but a small group of (type B and type AB) patients, and even incompatible patients can be given up to 4 units of plasma without ill effect. The same

is not true for RBC's, which when incompatible may illicit a potentially fatal Acute Immune Hemolytic Reaction.

- Plasma is good for 5 days after thawed. The thawed plasma used for this study will be received on day 1 or 2 and the Blood Bank staff will monitor this.

McGuire Biospecimen Processing

- Blood will be taken at 4 different time points: (1) In the field (drawn by EMS),) On arrival in the ED, (3) 8 hours post-injury, and (3) 24 hours post-injury
    - You will be responsible for taking the kit from the EMS team and asking a nurse to draw the ED draw, the tubes for the field draw should already be in the kit
    - Instruct the nurse to collect blood in tubes in this order: Blue – Gold – Lavender
    - For each draw, the blood will be acquired by the VECTOR RA and taken to McGuire Hall located on Clay St. across from the School of Pharmacy.
    - Call the Platelet Lab technician (828-7757) and tell them you are on your way after the draw has been completed
    - When you arrive at McGuire Hall, the technician will meet you on the steps
    - Hand over the completed tubes to the technician
    - Keep the kit contents for the 8-hour and 24-hour draw and confirm the hours for these draws with the technician
    - List the 8-hour and 24-hour draw windows on the VECTOR task calendar and alert whoever will be on during those draws that they need to occur
    - For the 8- and 24-hour draws, the VECTOR RA on duty will find the patient's location (using CERNER) and will go to the nurse and ask to have the draws completed
- losing.
- Patients normally first receive RBC's on arrival to ED where O positive and O negative blood is kept at all times. At present plasma has to be ordered and delivered from the Blood Bank before a patient can get it. This study aims to give trauma patients plasma at an earlier time point to improve overall outcomes and avoid the "triangle of death" (low pH, hypotension, hypothermia).
- Whole blood is essentially impossible to store which is why it is separated into components.

    - Follow the same procedure for contacting McGuire when you are ready to walk the samples over

Overall Study Information

The thought process behind this study is that trauma patients will benefit from receiving plasma in the field because it will ultimately more closely mimic the fluids that they are

CONTACT INFORMATION

Blood Bank – 628-7058
April Hord – Education Coordinator – 628-2567

Platelet Lab – 828-7757
Dr. Erika Martin – Lab Director

Appendix I: Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Regulatory Requirements ORP Human Research Protection Office (HRPO) Version: 15

Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP)
Human Research Protections Regulatory Requirements
ORP Human Research Protection Office (HRPO)
Version: 15 April 2013 Page 1 of 7

1. Department of Defense (DoD) Human Subjects Protection Regulatory Requirements

a. DoD regulations require that the DoD include specific language in contracts or other comparable agreements (e.g., grants, assistance agreements, and cooperative research and development agreements) that might include research involving human subjects. This language identifies the awardee requirements and responsibilities, and requires that any research involving human subjects supported by the award be approved by a DoD Human Research Protection Official (DHRPO) prior to implementation of the research.

b. The awardee is responsible for overseeing execution of the research and must include similar language in subcontracts that support research involving human subjects. In addition, this language:

(1) Allows DoD representatives to independently review and inspect the awardee's research. This may include access to identifiable information or protected health information (thus, subjects must be informed);

(2) Allows DoD representatives to prohibit research that is determined to present unacceptable hazards or is non-compliant with DoD regulatory requirements;

(3) Applies to all human subjects research, whether or not it is determined to be exempt from the regulations.

c. The DHRPO must perform an administrative review of the research before the activities that involve human subjects can begin (e.g., human subject recruitment and data collection). At a minimum, the DHRPO must:

(1) Concur with the extramural institution regarding activities they have determined to be either (a) research not involving human subjects; or (b) research involving human subjects that is exempt from the regulatory provisions of 32 CFR 219.

(2) Confirm the institution has a Federal assurance appropriate for the conduct of the non-exempt research involving human subjects in question. If DoD institutions are engaged in the extramural research, they must have a DoD Assurance.

(3) Review the research protocol for compliance with DoD Instruction (DoDI) 3216.02 “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research,” accept the IRB determination of level of risk, ensure that the study is compliant with applicable DoD regulatory requirements and approve the

Version: 15 April 2013 Page 2 of 7

protocol prior to implementation.

(4) Review and accept IRB-approved substantive changes to an approved research protocol before they are implemented.

(5) Ensure the IRB conducts an appropriate continuing review at least annually.

(6) When the research involving human subjects is being conducted in a foreign country, confirm all applicable national laws and requirements of the foreign country have been met and confirm the IRB considered the cultural sensitivities in the setting where the research will take place.

d. The USAMRMC ORP HRPO has designated approval authorities to meet the DHRPO approval requirement for DoD supported research.

2. Requirements for Approval of Extramural Human Subjects Research

a. Federal Assurance of Compliance. Each institution engaged in non-exempt human subjects research must have a current Department of Health and Human Services Office for Human Research Protection (OHRP) FWA or DoD Assurance. An IRB review by one of the IRBs listed on the institution’s assurance or identified in an Institutional Agreement for IRB Review must be provided. To avoid delays in the HRPO approval process, verify that the institutions engaged in the research have active assurances. The Institution’s IRB office or the HRPO can assist in determining if engaged institutions have active assurances and obtaining an assurance is required.

b. Investigator Qualifications. A CV or Biosketch of the Principal Investigator (PI) must be provided to the HRPO. Documentation of human subjects protection training (per local policy) for the Principal Investigator and all Associate Investigators (AIs) must be provided to the HRPO prior to approval. A description of roles and responsibilities of study personnel will be requested during the review process to assist in determination of which institutions are engaged in the research.

c. When applicable, the following DoD unique requirements must be addressed prior to approval:

(1) 10 United States Code 980. The requirements of Title 10 United States Code 980, which are applicable to DoD sponsored research, must be considered. 10 USC 980 requires that “Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless- (1) the informed

consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Note that the definition of experimental subject is found in DoDI 3216.02 and has a much narrower definition than human subject. Research with experimental subjects must involve an intervention or interaction where the primary purpose of the research is to collect data regarding the effects of the intervention or interaction.

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An individual not legally competent to provide informed consent (e.g., incapacitated individuals, cognitively impaired, minors) may not be enrolled as an experimental subject in a DoD-supported experiment unless participation in the research is intended to benefit each subject enrolled in the study, to include subjects enrolled in study placebo arms. Studies designed in a manner that permits all subjects to potentially benefit directly from medical treatment or enhanced surveillance beyond the standard of care can meet the 10 USC 980 requirements.

10 USC 980 is only applicable to certain intervention studies. It does not apply to retrospective studies, observational studies, blood draws, and tissue collections. Contact the HRPO for further clarification regarding applicability of 10 USC 980 to the proposed research project.

(2) Research Monitor. For research determined to be greater than minimal risk, DoDI 3216.02 requires that the IRB approve, by name, an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.

The research monitor's duties should be based on specific risks or concerns about the research. The research monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The research monitor may be identified from within or outside the PI's institution.

Research monitor functions may include:

• observing recruitment and enrollment procedures and the consent process for individuals, groups or units,

• overseeing study interventions and interactions,

• reviewing monitoring plans and UPIRTSO reports;

• overseeing data matching, data collection, and analysis

There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

At a minimum, the research monitor:

• may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;

• shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;

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• shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

A biographical sketch or CV and human subject's protection training for the research monitor must be provided. There should be no apparent conflict of interest and the monitor cannot be under the supervision of the PI or other investigators or research staff. If the duties of the research monitor could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the research monitor is not an agent of the covered entity), the PI's institution may require the identity and location of the research monitor to be described in the study Health Information Portability and Accountability Act authorization.

(3) Recruitment of Military Personnel. Civilian investigators attempting to access military volunteer pools are advised to seek collaboration with a military investigator who will be familiar with service-specific requirements.

A letter of support from Commanders of military facilities or units in which recruitment will occur or the study will be conducted will be requested by the HRPO. Some military sites may also require that each volunteer seek written permission from their supervisor prior to participation in research studies.

Special consideration must be given to the recruitment process for military personnel. The Chain of Command must not be involved in the recruitment of military personnel and cannot encourage or order Service members to participate in a research study. For greater than minimal risk research, DoDI 3216.02 requires that an ombudsman be employed when conducting group recruitment briefings with Active Duty personnel to ensure that they understand that participation is voluntary. The use of an ombudsman may be recommended in other situations as well, especially when young enlisted service members, who are trained to follow orders, are being recruited. Service members are trained to act as a unit, so peer pressure should also be considered and minimized if possible.

(4) Payment to Federal Employees and Military Personnel. Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation and may not exceed $50 per blood draw. They may not receive any other payment or non-monetary compensation for participation in a research study unless they are off duty or on leave during the time they are participating in the protocol.

(5) USAMRMC Required Protocol and Consent Form Language;

The following must appear in the consent form:

• A statement that the DoD or a DoD organization is funding the study.

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• A statement that representatives of the DoD are authorized to review research records.

• In the HIPAA Authorization or HIPAA authorization section of the consent form, representatives of the DoD must be listed as one of the parties to whom private health information may be disclosed.

• If the study involves the participation of a research monitor (as defined by DoDI 3216.02), consideration should be given as to whether the research monitor should also be listed in the HIPAA Authorization as one of the parties to whom private health information may be disclosed.

(6) For Development of Medical Products. Product information must be provided with the protocol submission. The HRPO will assess protocols involving medical products for applicability of FDA regulations. Additional documentation may be requested for investigational products. If the FDA, the IRB, or another regulatory office has determined that the protocol does not require an IND or IDE, provide any documentation available related to this determination.

3. USAMRMC ORP HRPO Submission and Administrative Review Process

a. DoD research programs submit proposals selected for funding to the USAMRMC ORP HRPO for human subjects protection regulatory review. A Proposal Submission Form, designed to facilitate the protocol review process, is also submitted for review. This submission form contains information that the USAMRMC funding program may need to solicit from the Proposal PI before the proposal is submitted to USAMRMC ORP HRPO.

b. Once the proposal and completed Proposal Submission Form have been submitted and triaged, a HRPO staff member will contact the Principal Investigator (PI) to provide the HRPO Protocol Submission Form and request the Institutional Review Board (IRB) approved protocol (or an estimate of when the protocol will be submitted for review).

The PI must complete the information requested on the Protocol Submission Form. Any information that is unknown at the time of protocol submission will be obtained during the review process.

c. When the IRB approved protocol and Protocol Submission Form are received, the project will be assigned to a Human Subjects Protection Scientist (HSPS). The HSPS will be the main HRPO point of contact for the PI for information regarding initial review and approval of the protocol, in addition to life cycle reporting requirements. The HSPS will review the protocol for compliance with federal, DoD and state or host nation regulatory requirements and assist the PI with addressing any outstanding issues prior to submission for final HRPO approval. If revisions to the protocol or consent form are required to bring the protocol into compliance, the revised documents must be approved by the IRB prior to HRPO approval.

d. For protocols involving multiple research sites and/or multi-institutional collaborations on a single study, the HRPO must review and approve site specific

documentation prior to participation in human research activities. Note: For protocols involving multiple institutions, the review will proceed much faster if a flow chart or map is provided that outlines the protocol and indicates how each institution is involved.

e. If the project involves execution of all or part of the research outside of the United States the HRPO must confirm all applicable host national laws and requirements of the foreign country have been met and confirm the IRB considered cultural sensitivities in the setting where the research will take place. The Principal Investigator must provide adequate information to the HRPO regarding national laws and requirements and the cultural context in which the research will take place. This information can be provided through completion of applicable sections of the HRPO International Research Submission Form, or through inclusion of applicable information in the protocol.

f. Standard reporting requirements to HRPO are outlined at the end of this document. Additional protocol specific reporting requirements may be included in the HRPO approval memorandum.

4. Reporting Requirements and Responsibilities of the Principal Investigator to the USAMRMC ORP HRPO

a. The protocol will not be initiated until written notification of approval of the research project is issued by the HRPO.

b. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.

c. The Principal Investigator must comply with the following minimum reporting requirements. Specific reporting requirements for the protocol will be included in the HRPO Approval Memorandum. Failure to comply could result in suspension of funding.

(1) Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc), significant change in study design (i.e. would prompt additional scientific review) or a change that could potentially increase risks to subjects.

(2) Any changes of the IRB used to review and approve the research will be promptly reported to the USAMRMC ORP HRPO.

(3) All unanticipated problems involving risk to subjects or others must be

promptly reported by telephone (301-619-2165), by email (

usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the Institutional Review Board (IRB), the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) A copy of the continuing review approval notification by the IRB of Record must be submitted to the HRPO as soon as possible after receipt. For greater than minimal risk research, a copy of the continuing review report approved by the IRB must also be provided. Please note that the HRPO also conducts random audits at the time of continuing review. Additional information and documentation may be requested at that time.

(6) The final study report, including any acknowledgement documentation and supporting documents, must be submitted to the HRPO when available.

(7) The knowledge of any pending compliance inspection/visit by the FDA, DHHS Office of Human Research Protections (OHRP), or other government agency concerning this research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any regulatory agencies including legal or medical actions and any instances

of serious or continuing noncompliance with the regulations or requirements, must be promptly reported to the HRPO.

Please Note: The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

For questions regarding the HRPO human research protocol review requirements email usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil or leave a voicemail at 301-619-2165 and a staff member will contact you.

19 SUPPLEMENTAL MATERIALS

All supplements that are relevant to the protocol, but are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments. These documents can be found on the study shared drive and can be accessed by key study personnel at any time.

Reynolds et al. Trials (2015) 16:321
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TRIALS

STUDY PROTOCOL Open Access

Prehospital use of plasma in traumatic hemorrhage (The PUPTH Trial): study protocol for a randomised controlled trial

Penny S. Reynolds[1*], Mary Jane Michael[1], Emily D. Cochran[1], Jacob A. Wegelin[2] and Bruce D. Spiess[1]

Abstract

Background: Severe traumatic injury and haemorrhagic shock are frequently associated with disruptions of coagulation function (such as trauma-induced coagulopathy TIC) and activation of inflammatory cascades. These pathologies may be exacerbated by current standard of care resuscitation protocols. Observational studies suggest early administration of plasma to severely-injured haemorrhaging patients may correct TIC, minimise inflammation, and improve survival. The proposed randomised clinical trial will evaluate the clinical effectiveness of pre-hospital plasma administration compared with standard- of-care crystalloid resuscitation in severely-injured patients with major traumatic haemorrhage.

Methods/design: This is a prospective, randomized, open-label, non-blinded trial to determine the effect of pre-hospital administration of thawed plasma (TP) on mortality, morbidity, transfusion requirements, coagulation, and inflammatory response in severely-injured bleeding trauma patients. Two hundred and ten eligible adult trauma patients will be randomised to receive either two units of plasma, to be administered in-field, *vs* standard of care normal saline (NS). Main analyses will compare subjects allocated to TP to those allocated to NS, on an intention-to-treat basis. Primary outcome measure is all-cause 30-day mortality. Secondary outcome measures include coagulation and lipidomic/pro-inflammatory marker responses, volume of resuscitation fluids (crystalloid, colloid) and blood products administered, and major hospital outcomes (e.g. incidence of MSOF, length of ICU stay, length of hospital stay).

Discussion: This study is part of a US Department of Defense (DoD)-funded multi-institutional investigation, conducted independently of, but in parallel with, the University of Pittsburgh and University of Denver. Demonstration of significant reductions in mortality and coagulopathic/inflammatory-related morbidities as a result of pre-hospital plasma administration would be of considerable clinical importance for the management of haemorrhagic shock in both civilian and military populations.

Trial registration: ClinicalTrials.gov: NCT02303964 on 28 November 2014

Keywords: Bleeding, coagulopathy, inflammatory markers, INR, massive hemorrhage, prehospital, shock, thawed plasma, TRALI, transfusion, trauma

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Background

Following severe traumatic injury, the immediate care priorities are control of bleeding and correction of the hypovolemia and tissue hypoperfusion that result from excessive blood loss and tissue injury. Massive hemorrhage (MH) requires surgical intervention for definitive hemostasis. However, trauma-related hemorrhagic shock is also a disease of ischemic cellular injury and death, resulting from coagulation disruption and inflammatory precursor activation [7, 15, 23]. Approximately 25 % of severely injured patients present with severely abnormal coagulation changes occurring within very few hours of injury [22]. This so-called trauma-induced coagulopathy (TIC) is associated with 4-fold increase in mortality, increased rates of late death from sepsis and multiple organ failure (MOF), and worsened outcomes from traumatic brain injury (TBI) [4, 5, 13]. Ischemic cellular injury resulting from uncorrected, persistent, and systemic hypoperfusion eventually leads to systemic inflammatory response syndrome and irreversible multi-system organ failure (MSOF). MSOF is a major cause of late mortality and morbidity following severe trauma, with a mortality rate of 50 % to 80 % [20].

To minimize irreversible cell damage and death, it follows that recognition of MH should occur as soon as possible after injury and as far upstream as possible from initiation of coagulopathy/inflammatory cascades. Unfortunately early recognition may not be easily achieved, especially if bleeding is primarily internal. In practice, the extent of hemorrhage and shock during the initial assessment stage is based on vital signs, primarily blood pressure, pulse rate, palpable radial pulses, and mentation [1]. However these are extremely variable, nonspecific, and very poor indicators of perfusion status [29]. Therefore choice of first-line resuscitation fluids will be essential for preempting some of the negative outcomes of unrecognized MH and shock.

There is increased interest in reviving prehospital use of plasma transfusions for severely injured hemorrhaging patients, especially if time to definitive care is long. Observational data suggest improved 6-hr outcomes but no overall survival advantage with prehospital blood product administration [17]. Better patient 30-d survival was associated with earlier (<4 hr) in-hospital administration of relatively high ratios of plasma to packed red blood cells (pRBC) in both civilian [10, 18] and military [3] trauma populations; meta-analysis supports early use of plasma but does not conclude that there are additional survival benefits of 1:1 over 1:2 plasma:pRBC transfusion ratios [2] In contrast, plasma transfusions have been associated with increased morbidity and mortality in other studies of trauma [21] and non-MH patients [24, 26, 27]. However, interpretations of data from these studies may be confounded by lack of standardization in hospital resuscitation protocols, changes in transfusion practice over the past decade, confounding-by-indication bias [19] and survivor bias [16].

At present there are no data either from systematic reviews [11] or from completed, prospective, randomized controlled clinical trials [19] to assess the efficacy of plasma transfusion alone. Further, there are no rigorous definitions of how early infusion must occur relative to injury in order to demonstrate benefit. This study will be one of three prehospital trials conducted in parallel that explicitly examines the effect of prehospital plasma transfusion on mortality and morbidity in civilian trauma patient populations.

Methods/Design

Study design

This study is a prospective, open-label, non-blinded, randomized clinical trial to quantify the effects of early prehospital administration of plasma on death, coagulation function, transfusion requirements, and other relevant clinical outcomes for seriously-injured trauma patients with massive bleeding. Trial flow per the Consolidated Standards of Reporting Trials (CONSORT) guidelines [25] is shown in Fig. 1.

Ethical oversight

The study was approved by the Virginia Commonwealth University Institutional Review Board (VCU-IRB Protocol Record HM14813), Food and Drug Administration (FDA) (IND no. 15910); and the US Department of Defense (HRPO Log Number A-17160). The study was listed with the Clinical Trials register on 28 November 2014 (ClinicalTrials.gov number NCT02303964).

Study population

The study population consists of adult, physiologically unstable, polytrauma patients transported to Virginia Commonwealth University Medical Center (VCUMC), a Level I trauma center. The catchment area is Henrico County and City of Richmond, Virginia. Henrico Fire EMS system (HFD) serves a population of 325,000 with over 30,000 transports per year; the city of Richmond EMS system (Richmond Ambulance Authority, RAA) serves a metro area of 222,000 with over 27,000 transports per year.

Inclusion criteria

Patients eligible for this study include all adult (≥18 years) patients of either sex, with blunt and/or penetrating trauma with multi-system injuries and unstable vital signs (systolic blood pressure (SBP) ≤70 mmHg, or SBP 70–90 mmHg with heart rate (HR) ≥108 beats per minute (bpm)), indicative of severe ongoing hemorrhage.

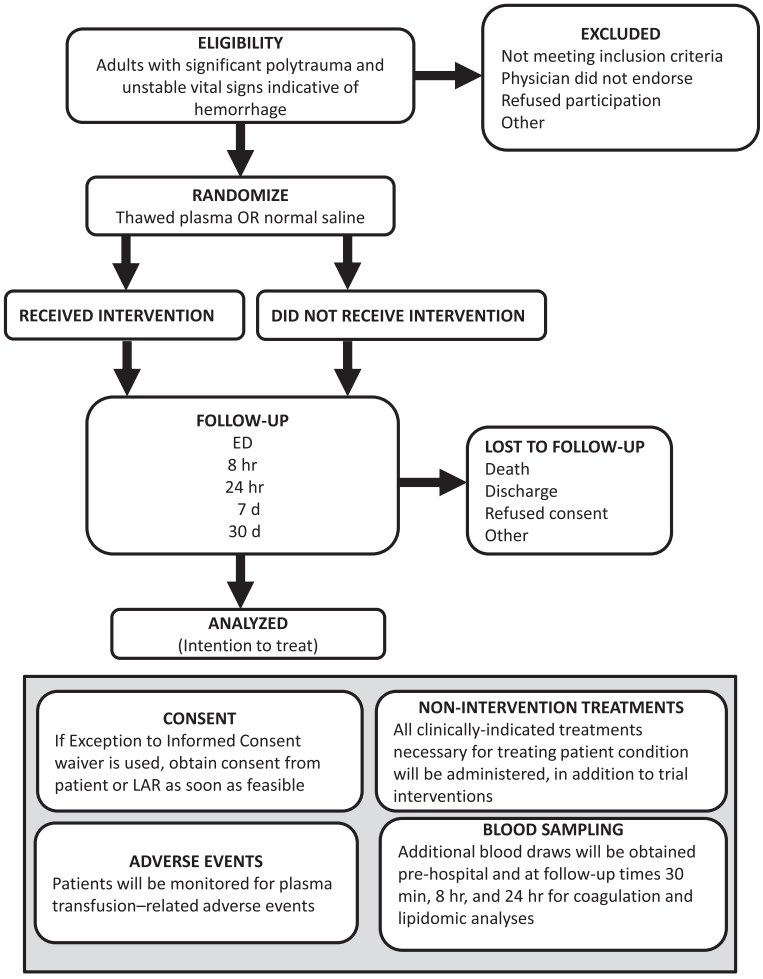

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of phase progress for the Virginia Commonwealth University (VCU) plasma trial (PUPTH), a parallel randomized trial of prehospital administration of plasma vs standard-of-care normal saline in a trauma population. *ED* Emergency Department

Exclusion criteria are: (1) presence of an opt-out wrist band, wallet card, Medical Alert jewelry, bracelet, or similar identifier to indicate Jehovah's Witness or similar patient group objecting to transfusion of blood and/or blood products; (2) refusal of consent by patient or legally appointed representative (LAR); (3) language barrier (non-English or non-Spanish speaking); (4) not expected to survive transport to VCUMC (based on extreme severity of injuries, on-scene cardiac arrest, and/or cardiopulmonary resuscitation (CPR) prior to randomization); (5) documented do not resuscitate (DNR) order; (6) isolated penetrating head trauma; (7) burns to >20 % of the body surface; (8) pregnancy; (9) prisoner; (10) if patient transport has proceeded before arrival at the scene by the emergency medical services (EMS) supervisor with plasma, and (11) failure of the EMS to obtain intravenous (IV) access.

Patient drop-out

Patients may refuse consent and leave the study at any time for any reason. Subjects can be withdrawn from the study emergently by the attending study physician if they develop signs and symptoms of acute transfusion reaction.

Interventions and controls

Patients will be randomized prior to arrival at the Emergency Department (ED) to receive either thawed fresh-frozen plasma (TP) or standard-of-care normal saline (NS) during prehospital transport. Patients randomized to the TP arm will receive up to two units of pre-thawed A+ plasma. The control intervention is standard-of-care NS administered IV/intra-osseous (IO) per prehospital (ODEMSA) protocol to maintain SBP at 90–100 mmHg.

The VCUMC Blood Bank will provide plasma to EMS supervisors. Use of low-titer anti-B (<1:100) A+, rather

than AB (universal donor), plasma is justified on the grounds of the scarcity of AB plasma, and because of the extremely small risk of hemolytic reaction associated with administering A+ to patients who are not blood group compatible (incidence 0.1–1 %) [9]. TP will be maintained in dedicated refrigeration units in the EMS supervisor vehicle; unused TP will be exchanged within 24 hr to the VCUMC Blood Bank.

Randomization

Eligible patients will be randomly assigned to receive either TP or NS prior to ED arrival. Randomization codes will be generated using complete randomization; code sequence is secured by trial statisticians, and held at the VCUMC Transfer Call Center in sealed opaque envelopes. Patients will be screened for eligibility by on-scene prehospital providers. Endorsement for plasma administration will be given by the study physician on call. At this point the patient is considered enrolled into the study. Transfer Centre personnel will then open the next envelope in sequence and advise EMS as to patient allocation.

Study outcomes

The primary outcome of this study will be all-cause 30-day mortality. Secondary outcomes are: (1) hemodynamics (specifically SBP, mean arterial pressure (MAP), and HR); (2) cumulative volume of resuscitation fluids and blood products utilized at 8 and 24 hr from injury (volumes of crystalloid and/or colloid, units of red blood cells, units of plasma, doses of platelets, doses of cryoprecipitate); (3) hematology (hemoglobin (Hb) and hematocrit (Hct)) and blood biochemistry (pH, lactate, base deficit, and bicarbonate); (4) coagulation function (thromboelastography (TEG), fibrinogen, FV, FVIII, prothrombin time (PT), activated partial prothrombin time (aPTT), von Willebrand's factor, D-dimer, PFA-100, and platelet count); (5) lipidomic profile (arachidonic acid, eicosanoid, and prostacyclin expression); (6) hospital outcomes on days 7 and 30 (rates of MSOF, rates of acute renal failure (ARF), number of surgeries, number of infections, duration of mechanical ventilation, length of ICU stay, and length of hospital stay).

Other data

Patient demographics (age, sex, height, weight, past medical history, comorbidities, medications), mechanism of injury, injury severity assessments—Glasgow coma score (GCS), injury severity score (ISS), sequential organ failure assessment (SOFA), and acute physiology and chronic health evaluation (APACHE IV), routine vital signs and laboratory data, hospital-care-mandated medications and interventions (e.g., intubation, mechanical ventilation, chest thoracotomy, and needle decompression, etc.)—will be collected from individual medical records as they become available after patient admission.

Timelines

Follow up of patients enrolled in the trial ends at death or 30 days post-randomization, whichever occurs first. Patients discharged before 30 days will be followed up via telephone by designated study personnel. Blood samples for coagulation function and lipidomic profiling will be collected from each patient at four pre-specified time points: prehospital (close to point of injury, and before prehospital resuscitation), in the ED (approximately 30 min from hospital admission), and at 8 and 24 hr from admission.

Estimated event rate and sample size calculations

VCU Trauma Center registry data suggest that 30-day mortality under the standard-of-care protocol is between 16.4 % and 29.2 %; this is similar to the estimated 26 % mortality for the control arm of the Resuscitation Outcomes Consortium (ROC) prehospital hypertonic saline trial [6]. Assuming 24 % mortality in the control group, a sample size of 105 per arm will achieve 80 % power to detect a clinically significant reduction in mortality of 60 % (9.6 % mortality) in the plasma group [12].

Disclosure, consent, and confidentiality protection

Community consultation and public disclosure procedures

Pre-trial public disclosure (required by 21 CFR 50.24) was completed in 2013–2014. Information was disseminated by community meetings, web-based and social media outlets, paid advertisements, and media news releases to TV, radio, and newspapers. Public disclosure included a summary of investigational plans, background information about the study, a synopsis of the protocol and study design, risks and benefits of plasma versus the standard crystalloid fluid, subject selection, exception from informed consent requirements, procedures for contacting LARs, and procedures for declining participation in the study. Following study termination, findings of the clinical trial will be disseminated to the community by media news releases, the trial website (http://www.cctr.vcu.edu/news/feature/plasma.html), and relevant patient organizations.

Consent procedures

Significant multi-system trauma with either overt or occult massive hemorrhage is a life-threatening emergency. As treatment must be initiated as early as possible, and severely injured patients may be either unable or not competent to give fully informed consent, this trial will be conducted under the Exception from Informed Consent Requirement (21 CFR 50.24). However all reasonable attempts to impart trial information and obtain

consent will be made, depending on the urgency of the immediate medical situation, the mental status of the patient, and the availability of an LAR or next of kin.

After patient admission, and if the patient is unable to consent, attempts to contact the LAR or adult next of kin will be initiated (1) no later than 30 min post-ED arrival, then (2) every 30 min for 2 hr, (3) at least three more times for the remainder of the first 24 h, (4) at least twice a day through the end of day 7, and (5) at least once per week through the end of day 30, death, or discharge.

Confidentiality will be maintained by securing paper-based records in a central secure location and electronic records by access controls and encryption, both to be accessed only by authorized study personnel. All records will be de-identified and data coded with the key stored in a separate secure location.

Post-randomization treatment

All clinically indicated treatments (including blood product and fluid administration) will be given as appropriate per attending physician discretion. Standard of care for polytrauma patients with MH includes administration of TP plus blood products and/or crystalloid and colloid shortly after reaching VCUMC ED, unless otherwise indicated. In addition to administration of trial resuscitation treatments (TP or NS), trial-specific interventions will include blood sampling for coagulation function and lipidomic determinations; Approximately 20 mL of blood will be obtained from each patient at four time points.

Trial management

Stopping rules

It is expected that the trial will terminate when the intended sample size has been achieved. However, the trial will be stopped prior to completion if: (1) the intervention is associated with adverse effects that call into question the safety of the test intervention; (2) problems with study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information that becomes available during the trial necessitates discontinuation of the trial. The Principal Investigator (PI) will include an assessment of futility in the annual progress report to the FDA (using statistical means such as predictive probability, if appropriate), and will consult with the Data and Safety Monitoring Board (DSMB) to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

Trial Steering and Trial Management Committees

The Trial Management Committee consists of the Trial Steering Committee members plus a Trial Data Manager, and Trial Financial Administrator (Table 1). Responsibilities include (but are not limited to: (1) maintenance of trial records; (2) confirmation of regulatory approval compliance before the start of the trial; (3) provision of trial-specific training; (4) provision of specialized trial materials; (5) data management and security; (6) regular communication with collaborators as to study progress; (7) safety reporting; (8) statistical analyses, and (9) publication and dissemination of trial results.

Publication and dissemination of results

The trial protocol and results will be published in peer-reviewed journals. All publications will follow the CONSORT statement [25]. Credit for the study will be assigned to collaborators who have actually performed designated work. Links to published data will be provided through the ClinicalTrials.gov website. The results of the trial will be reported first to trial collaborators.

Table 1 Members of the Prehospital use of plasma in traumatic hemorrhage (PUPTH) Trial Steering and Management Committees

Name	Affiliation	Role
Bruce D Spiess, MD	Department of Anesthesiology	Principal Investigator
Mary-Jane Michael, RN, MS	Department of Anesthesiology	Trial Coordinator
Chris Hogan, MD	Department of Emergency Medicine and Trauma Surgery	Clinical expert
Joseph P Ornato, MD	Department of Emergency Medicine	Clinical expert
Ron Daniel, MD	Department of Anesthesiology	Trial Safety Officer
Penny S Reynolds, PhD	Department of Anesthesiology	Trial expert
Emily Cochran, RN, MS	Department of Anesthesiology	Trial expert
Jacob Wegelin, PhD	Department of Biostatistics	Trial Statistician
Brian Bush, PhD	Department of Biostatistics	Data management, IT
Carolyn Jeter	Department of Anesthesiology	Financial administration
William Aiken, Capt.	Henrico Department of Fire	EMS
Wayne Barbour	Richmond Ambulance Authority	EMS
Solomon Luckett	Richmond Ambulance Authority	EMS

Dissemination of results to patients will take place via the media, relevant patient organizations, and the trial website (http://www.cctr.vcu.edu/news/feature/plasma.html).

Safety and adherence oversight

Data Safety Monitoring Board (DSMB) oversight

An independent DSMB has been appointed to oversee safety monitoring and trial data (Table 2). DSMB duties and responsibilities are outlined in the DSMB Charter tailored specifically for this trial and outlined in accordance with charter guidelines proposed by the DAMOCLES Study Group [8]. The DSMB will review cumulative data at regular intervals over the course of trial, and advise the TSC apropos the safety of both currently enrolled subjects and those to be recruited. The trial may be terminated early by the Trial Steering Committee and Trial Safety Officer on recommendation from the DSMB. Study stopping criteria include futility (significantly increased risk of serious adverse effects in one of the treatment groups based on prespecified stopping boundaries for the primary outcome) and lack of feasibility (e.g., extremely low patient recruitment, excessive patient dropout, etc.).

Adverse events

Adverse transfusion-related events are extremely rare in the USA (0.24 % in 2011). Clinical events that are considered transfusion reactions include: fever (body temperature change >2 °C), urticaria, pruritis, flushing, hypotension, respiratory distress, bronchospasm, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO) [28].

Study progress and safety will be reviewed weekly by the Safety Oversight Officer. Assessment and reporting progress reports will be provided to DSMB; these reports will include numbers for patient recruitment, retention, attrition, and adverse events (AE) and serious adverse events (SAE). All reported AE will be assessed for relationship to the study intervention, reviewed as to treatment arm and further classified by severity (mild, moderate, severe, life threatening, or disabling), probability (expected vs unexpected), actions taken, and resolution, and will be reported to VCU-IRB.

Protocol adherence

Data on adherence to the study protocol will be collected weekly by research staff and reviewed quarterly by the PI and the Safety Officer. Weekly adherence will be evaluated by EMS supervisors and the Trial Safety Officer by monitoring four adherence criteria for each enrolled patient: (1) patient met inclusion criteria, (2) patient was appropriately randomized, (3) patient received appropriate fluid, and (4) patient had prehospital blood samples drawn. Scene and transport times are obtained routinely in both EMS systems, and if feasible will be compared to non-protocol case times to assess if protocol adherence results in unusual delays in time to definitive care. If adherence falls below the suggested rate of 80 %, which might affect study integrity in terms of testing the primary hypotheses, the Safety Officer will suggest a conference call for study investigators and EMS personnel to discuss methods for improving adherence. Adherence and deviations from the study standard operating procedure (SOP) will be reported to the Trial Coordinator and the VCU-IRB.

Data management

The VCU Biostatistics Data Coordinating Group created standard data entry procedures and systems for web-based data management during the community consultation phase of the PUPTH trial (completed in 2013), and will continue to oversee data collection, data entry, and data quality assurance. This trial will utilize the REDCap platform for data collection and storage [14]. Staff will coordinate with the University Computer Center to back up and archive data daily, and generate reports as required by the investigators.

Data analyses

Primary analyses will compare primary and secondary outcomes of patients assigned to either TP or NS on an intention-to-treat basis. Definitive analyses will occur after the 30-day observation period for all survivors in each arm has been completed. Data will be assessed on de-identified data by statisticians and data analysts blinded to patient randomization and allocation category. Appropriate analysis strategies to reduce effects of survival and time-dependencies in post-admission treatments will be applied as necessary.

Planned subgroup analyses will be stratified on: (1) primary mechanism of injury (blunt or penetrating); (2) injury severity (severe ISS 16–24, critical ISS ≥ 25); (3) presence or absence of traumatic brain injury, defined by GCS categories (severe 3–8, moderate 9–12, mild/absent

Table 2 Members of the independent Data Safety and Monitoring Committee

Name	Affiliation	Expertise
Neil Blumberg, MD	University of Rochester Medical Center, New York	Clinical expert, DSMB chair
Kevin R Ward, MD	University of Michigan School of Medicine, Michigan	Clinical expert
Rao Ivatury, MD	Virginia Commonwealth University Medical Center, Richmond, Virginia	Clinical expert
Roy Sabo, PhD	Virginia Commonwealth University School of Medicine, Virginia	Independent statistician

13–15) or by abbreviated injury score-head (AIS-H) categories (yes ≥3; no <3); (4) presence or absence of severe shock/tissue hypoperfusion (yes defined by base deficit ≥6 and lactate ≥3 mmol/L; no otherwise). Interaction tests will be used to examine the effect of the intervention (if any) across subgroups.

Interim analyses: there will be three planned analyses. Two interim analyses will be performed following accrual of 70 patients (35 per arm) and 140 patients (70 per arm), respectively. Interim and final data will be submitted to the DSMB for review; stopping criteria are based on safety data (see *Stopping rules*). Records will be assessed for data quality, including completeness (thereby encouraging collection of high-quality data), rates of recruitment and losses to follow up, and rates of protocol compliance.

Discussion

Benefit of early in-hospital use of TP to correct trauma-related coagulation dysfunction is weakly supported by several observational studies [2], but unsupported or contradicted by other studies [21, 27]. However, confounding bias inherent to such studies, coupled with elastic definitions of what constitutes early in the critical care timeline, means that these data are not particularly informative with respect to the immediate care of critically injured patients in hemorrhagic shock. This study is designed to assess the efficacy of prehospital plasma resuscitation on clinically relevant endpoints of mortality and short-term coagulation and inflammatory response.

There are several limitations to this study: TP infusion cannot be blinded to prehospital providers (although subsequent healthcare professionals may not necessarily receive this information), variable scene–hospital transport times of 6–30 min, so that not all patients allocated to the TP arm will receive the full complement of two units of TP before hospital arrival, and the complexity of patient management in the field, which means that the prehospital period will be most vulnerable to missing data.

This trial, coupled with those at Pittsburgh and Denver sister institutions, will be among the first to test the hypothesis that prehospital plasma administration to severely injured patients is effective in reducing trauma-related mortality and coagulopathy. Resulting data will be of considerable clinical importance for informing the management of hemorrhagic shock in both civilian and military populations.

Trial status

The trial has begun enrolling patients. The expected average enrollment rate is one patient per week until 2016.

Abbreviations

AABB: American Association of Blood Banks; AIS-H: abbreviated injury score-head; APACHE IV: acute physiology and chronic health evaluation IV score; aPTT: activated partial prothrombin time; bpm: beats per minute; DNR: do not resuscitate; DoD: Department of Defense; DSMB: data safety monitoring board; ED: Emergency Department; EMS: emergency medical services; FDA: Food and Drug Administration; FFP: fresh-frozen plasma; GCS: Glascow coma score; Hct: hematocrit; HFD: Henrico Department of Fire; Hb: hemoglobin; HR: heart rate; HS: hypertonic saline; IND: Investigational New Drug; ISS: injury severity score; LAR: legally authorized representative (according to Code of Virginia Definition 32.1-162.16); MAP: mean arterial pressure; MH: massive hemorrhage; MSOF: multi-system organ failure; NIH: National Institute of Health; NS: normal saline (0.9 % NaCl solution); PI: Principal Investigator; PT: prothrombin time; PUPTH: Prehospital use of plasma in traumatic hemorrhage; RAA: Richmond Ambulance Authority; RBC: red blood cells; ROC: Resuscitation Outcomes Consortium; SBP: systolic blood pressure; SC: Study Coordinator; SOFA: sequential organ failure assessment; SOP: standard operating procedure; TACO: transfusion-acquired circulatory overload; TBI: traumatic brain injury; TCCC: Tactical Combat Casualty Care; TEG: thromboelastography; TIC: trauma-induced coagulopathy; TRALI: transfusion-related acute lung injury; VCUMC: Virginia Commonwealth University Medical Center.

Competing interests

The authors have no conflicts of interest to declare. The success or failure of this study has no financial or commercial implications that could be construed as having benefit to those involved in the study outside of their job descriptions as supported by the grant from the United States Army.

Authors' contributions

BDS designed and drafted initial versions of the study protocol; MM wrote the final versions of the clinical protocol and obtained authorization from the ethics committees, EDC contributed to writing the study protocol SOPs and amendments, JAW was responsible for the statistical design and power analyses, and PSR contributed to drafting the study protocol and protocol SOPs, and wrote the manuscript. All authors have provided critical revisions to the protocol for important intellectual content and have approved the final version to be used in this trial.

Authors' information

PSR is Research Assistant Professor (Anesthesiology, VCUMC). MJM (RN, MS) is the PUPTH Trial Coordinator and Research Program Manager. EDC (RN, MS) is Chief Regulatory officer for the PUPTH trial. JAW (PhD) is Assistant Professor (Biostatistics, VCUMC) and trial statistician. BDS is Professor of Anesthesiology at VCUMC and Principal Investigator of the PUPTH trial.

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From: IRBPANELC@VCU.EDU
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Date: Thursday, July 30, 2015 05:20PM
Subject: Notification: IRB HM14813_CR2 Spiess - IRB Correspondence

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TO: Bruce Spiess

CC: Emily Cochran
Mary Michael

FROM: IRB Panel C

RE: Bruce Spiess ; IRB HM14813_CR2 Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PUPTH)

On 7/30/2015 this research study was ***approved for continuation*** according to 45 CFR 46.108(b) and 45 CFR 46.109(e) by VCU IRB Panel C .

The information found in the electronic version of this study's smart form and uploaded documents now represents the currently approved study, documents, informed consent process, and HIPAA pathway (if applicable). Please see instruction box below for details on viewing the approved study.

Notes from the IRB: At the next continuing review submission; please include a written report summarizing each of the following items listed:

1. Any complaints and phone calls received;

2. Patient outcomes and benefits;

3. The attempts made to elicit refusal and to contact LARs/family members for each participants;

4. The number of patients the study attempted to enroll, the number or refusal and withdrawals, and number of patients actually enrolled;

5. The implementation of any public disclosure activities during this approval period.

This study is approved for either a period of 6 months or until 5 patients have been enrolled, whichever occurs first. This approval expires on 1/21/2016. Federal Regulations/VCU Policy and Procedures require continuing review prior to continuation of approval past that date. Continuing Review notices will be sent to you prior to the scheduled review.

If you have any questions, please contact the Office of Research Subjects Protection (ORSP) or the IRB reviewer(s) assigned to this study.

The reviewer(s) assigned to your continuing review will be listed in the History tab and on the continuing review workspace. Click on their name to see their contact information.

Attachment – Conditions of Approval

Conditions of Approval:

In order to comply with federal regulations, industry standards, and the terms of this approval, the investigator must (as applicable):

1. Conduct the research as described in and required by the Protocol.

2. Obtain informed consent from all subjects without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate (unless Waiver of Consent is specifically approved or research is exempt).

3. Document informed consent using only the most recently dated consent form bearing the VCU IRB "APPROVED" stamp (unless Waiver of Consent is specifically approved).

4. Provide non-English speaking patients with a translation of the approved Consent Form in the research participant's first language. The Panel must approve the translated version.

5. Obtain prior approval from VCU IRB before implementing any changes whatsoever in the approved protocol or consent form, unless such changes are necessary to protect the safety of human research participants (e.g., permanent/temporary change of PI, addition of performance/collaborative sites, request to include newly incarcerated participants or participants that are wards of the state, addition/deletion of participant groups, etc.). Any departure from these approved documents must be reported to the VCU IRB immediately as an Unanticipated Problem (see #7).

6. Monitor all problems (anticipated and unanticipated) associated with risk to research participants or others.

7. Report Unanticipated Problems (UPs), including protocol deviations, following the VCU IRB requirements and timelines detailed in VCU IRB WPP VIII-7);

8. Obtain prior approval from the VCU IRB before use of any advertisement or other material for recruitment of research participants.

9. Promptly report and/or respond to all inquiries by the VCU IRB concerning the conduct of the approved research when so requested.

10. All protocols that administer acute medical treatment to human research participants must have an emergency preparedness plan. Please refer to VCU guidance on http://www.research.vcu.edu/irb/guidance.htm.

11. The VCU IRBs operate under the regulatory authorities as described within:

a) U.S. Department of Health and Human Services Title 45 CFR 46, Subparts A, B, C, and D (for all research, regardless of source of funding) and related guidance documents.
b) U.S. Food and Drug Administration Chapter I of Title 21 CFR 50 and 56 (for FDA regulated research only) and related guidance documents.
c) Commonwealth of Virginia Code of Virginia 32.1 Chapter 5.1 Human Research (for all research).

Conditions of Approval (version 010507)