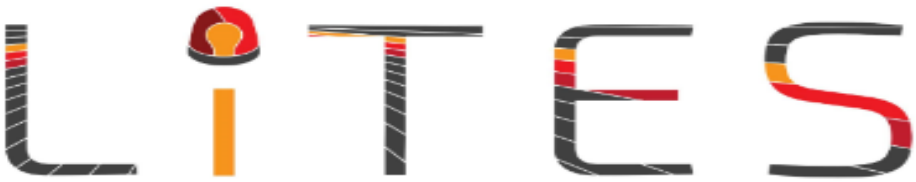


Linking Investigations in Trauma and Emergency Services

Task Order 0004

Cold Stored Platelet Early Intervention in Hemorrhagic Shock (CriSP-HS) trial

Version 7: 12/17/2021

Contents

Protocol Synopsis

Protocol Title:	Cold Stored Platelet Early Intervention in Hemorrhagic Shock (CriSP-HS) Trial
Protocol Number:	STUDY21100002
NCT Number:	NCT04667468
Version # and Date:	Version 7 dated 12/17/2021
Investigational Drug:	Cold Stored Platelets
Trial Sites:	Clinical Coordinating Center • University of Pittsburgh, University of Pittsburgh Medical Center, PI Jason Sperry, Co-PI Frank Guyette Additional Sites: • Baylor College of Medicine, PI Chad Wilson • University of Mississippi, PI Matthew Kutcher • University of California San Francisco, PI Lucy Kornblith • University of Southern California, PI Kenji Inaba • University of Texas Health Sciences Center Houston, PI Bryan Cotton • MetroHealth, PI Jeffrey Claridge (alternate)
Funding Agency	Department of Defense
IND Sponsor:	Jason L Sperry, MD, MPH
Study Aims:	**AIM#1:** Determine the feasibility, most appropriate study population and primary outcome that will lead to a large multicenter clinical trial designed to evaluate the effectiveness of cold stored platelet early intervention in patients with injury and hemorrhagic shock. **AIM#2:** Determine whether early cold stored platelet infusion compared to standard care results in improved clinical outcomes and hemostatic function in injured patients with hemorrhagic shock. **AIM#3:** Determine if early cold stored platelet hemostatic function is similar at 1 through 7 days as compared to 8 through 14 days in patients with hemorrhagic shock.
Study Design:	Open label, multi-center, randomized trial designed to determine the feasibility, efficacy and safety of urgent release cold stored platelets in patients in hemorrhagic shock
Planned Sample Size:	200

Planned Study Time:	3-year study with 2 years of enrollment
Major Inclusion Criteria:	Patients with traumatic injury who meet the following criteria: 1) Has 2 or more of any of the following: a. Hypotension (systolic blood pressure ≤ 90 mmHg) in the prehospital or emergency department setting, b. Penetrating mechanism, c. Abdominal or Extended FAST ultrasound is positive or equivocal or deferred by clinical team due to emergent visit to Interventional Radiology or a need for emergent laparotomy, thoracotomy, or vascular exploration d. Heart Rate ≥ 120 in the prehospital or emergency department setting. **AND** 2) Clinical team deems Operating Room (laparotomy, thoracotomy or vascular exploration) or Interventional Radiology for embolization within 60 minutes of arrival to be clinically indicated.
Major Exclusion Criteria:	1. Wearing "NO CriSP" opt–out bracelet 2. Age > 90 or < 15 years of age 3. Isolated fall from standing injury mechanism 4. Prisoner 5. Pregnant 6. Traumatic arrest with > 5 minutes of CPR without return of vital signs 7. Brain matter exposed or penetrating brain injury (GSW) 8. Isolated drowning or hanging victims 9. Isolated burns > estimated 20% total body surface area 10. Objection to study voiced by subject or family member in Emergency Department
Primary Endpoint:	Feasibility

I. Specific Aims

Resuscitation strategies for the acutely injured patient in hemorrhagic shock have evolved with patients benefitting from receiving less crystalloid and early red blood cell use with balanced ratios of plasma and platelets.[1-3] These resuscitation practices have been termed Damage Control Resuscitation and have been incorporated into massive transfusion protocols in level 1 trauma centers across the country.[2-4] Despite these changes, deaths from traumatic hemorrhage continue to occur in the first hours following arrival at the trauma center, underscoring the importance of early interventions which provide benefit.[1-3,5] Platelet transfusions are a vital component of

damage control resuscitation and are essential to early hemostasis.[3,6-8] Currently, platelets are not available in the prehospital or early resuscitation setting and are typically provided only after massive transfusion protocols are initiated, beyond the early phase of care for hemorrhagic shock patients.[9]

Platelet use in far forward environments are not available due to logistical storage and shelf life requirements. Cold-stored platelets can be refrigerated similar to red blood cells and plasma units and may be less prone to bacterial contamination. Growing evidence suggests that cold-stored platelets have superior hemostatic capabilities.[7,9-12] For patients in hemorrhagic shock, cold stored platelets may be beneficial in an urgent release fashion soon after arrival to the trauma center as compared to current standard care. Currently there is no high-level clinical trial evidence demonstrating the safety and efficacy of urgent release cold stored platelet transfusion following injury. The aims of the Cold Stored Platelet early intervention in hemorrhagic shock (CriSP-HS) pilot trial are to determine the feasibility, efficacy and safety of urgent release cold stored platelets in patients in hemorrhagic shock.

AIM#1: Determine the feasibility, most appropriate study population and primary outcome that will lead to a large multicenter clinical trial designed to evaluate the effectiveness of cold stored platelet early intervention in patients with injury and hemorrhagic shock.
AIM#2: Determine whether early cold stored platelet infusion compared to standard care results in improved clinical outcomes and hemostatic function in injured patients with hemorrhagic shock.
AIM#3: Determine if early cold stored platelet hemostatic function is similar at 1 through 7 days as compared to 8 through 14 days in patients with hemorrhagic shock.

Hypothesis for clinical outcomes

Early infusion of cold stored platelets as compared to standard care will result in a reduction in 3-hour mortality, 24-hour mortality, in hospital mortality, 30-day mortality, lower death from hemorrhage, reduced blood and blood component transfusion requirements in the initial 24 hours, a lower incidence of acute respiratory distress syndrome (ARDS), a reduced time to hemostasis, a lower incidence of coagulopathy, improved hemostatic and platelet function and a similar rate of allergic/transfusion reactions and incidence of transfusion related acute lung injury in patients with injury and hemorrhagic shock.

II. Background and Significance

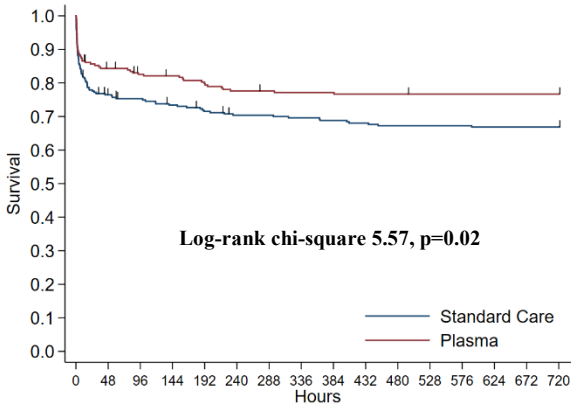
The acute management of the severely injured patient with hemorrhage following trauma center arrival has evolved over the last decade.[2,13]

Current treatment priorities include prevention of coagulopathy through minimization of crystalloid and early blood component resuscitation including plasma and platelets in equal ratios with packed red blood cells.[3] These in-hospital practices, termed damage control resuscitation, are widely used in both battlefield and civilian resuscitation following traumatic injury.[2,3,14,15]

Initiation of the tenets of damage control resuscitation early, soon after arrival, has the potential to reduce downstream complications attributable to hemorrhage by intervening closer to the time

of injury, prior to the development of coagulopathy; irreversible shock; and the ensuing inflammatory response.[16-19] Other blood constituents have recently been shown to be beneficial when given early. Thawed plasma transfusion has been shown to safely reduce 30-day mortality when infused early, in the prehospital setting, in patients at risk of hemorrhagic shock and this separation of survival occurs within the first 3 hours. (**Figure 1**.) Platelet transfusion is associated with improved outcomes in the acutely bleeding patients.[6-8] Cold Stored Platelets have been reported to reduce blood loss when provided for hemorrhage and are a more effective hemostatic product.[7,12,20]

Figure 1. 30-day survival analysis



Cold stored platelets are less likely to become bacterial contaminated and were the standard of care platelet product until the 1980s.[9,21,22] Despite this history and potential benefits, the risks associated with urgent release cold stored platelets and their respective efficacy and function over time are not known in patients with hemorrhagic shock.

By providing Cold Stored Platelets in an urgent release fashion following injury, a potentially superior hemostatic agent is given early, closer to the time of injury. The current pilot trial was designed to determine the feasibility, efficacy and safety of urgent release cold stored platelets as compared to standard care in injured patients in hemorrhagic shock. There are no high-level data which appropriately characterize the urgent release use of cold stored platelets out to 14 days or their function over that time period as compared to standard room temperature platelets. These results will be able to inform future large randomized clinical trials allowing the most appropriate injured population, inclusion criteria, and primary outcome to be selected and utilized.

III. Study Design/Setting

The current proposed pilot study will be a 3-year, multi-center, open label, randomized trial utilizing 5 level-1 trauma centers from within the LITES network and will enroll approximately 200 patients. The University of Pittsburgh will be the Clinical Coordinating Center and the Data Coordinating Center for the study.

Study Population**:** Blunt or penetrating injured patients with hemorrhagic shock requiring operative management.

Inclusion Criteria

Patients with traumatic injury who meet the following criteria:

3) Has 2 or more of any of the following:

a. Hypotension (systolic blood pressure ≤ 90 mmHg) in the prehospital or emergency department setting,
b. Penetrating mechanism,
c. Abdominal or Extended FAST ultrasound is positive or equivocal or deferred by clinical team due to emergent visit to Interventional Radiology or a need for emergent laparotomy, thoracotomy, or vascular exploration
d. Heart Rate ≥ 120 in the prehospital or emergency department setting.

AND

4) Clinical team deems Operating Room (laparotomy, thoracotomy or vascular exploration) or Interventional Radiology for embolization within 60 minutes of arrival to be clinically indicated.

Exclusion Criteria

1. Wearing "NO CriSP" opt–out bracelet
2. Age > 90 or < 15 years of age
3. Isolated fall from standing injury mechanism
4. Known prisoner or known pregnancy
5. Traumatic arrest with > 5 minutes of CPR without return of vital signs
6. Brain matter exposed or penetrating brain injury (GSW)
7. Isolated drowning or hanging victims
8. Isolated burns > estimated 20% total body surface area
9. Objection to study voiced by subject or family member in Emergency Department

Study Intervention

One apheresis unit issued per site standard protocol will represent the CSP intervention. The volume of the intervention will be approximately 300ml and will be stored in an FDA monitored approved refrigerator at 1-6 degrees Celsius for up to 14 days from preparation. CSP units will be clearly and specifically labeled as investigational product to avoid inadvertent clinical use.

Study Intervention Arm**:** Patients randomized to the study intervention arm will receive an early infusion of urgent release cold stored platelets (CSP) once the patient meets all inclusion and no exclusion criteria. CSP infusion will be initiated by the clinical team, under the direction of the study team, in the Emergency Department or during transport to the operating room (OR) or interventional radiology (IR) suite. For those patients who initially lack IV access, CSP infusion will occur once IV access is obtained irrespective of location. CSP infusion should be initiated first when possible but can be infused concomitantly with other transfusion requirements per institutional standard care.

Standard Care Arm**:** Patients randomized to the standard care arm will receive resuscitation, blood and blood component transfusion per site standard care.

Randomization and Masking

Individual patients meeting all inclusion and no exclusion criteria in the emergency department will be randomized and assigned according to a 1:1 ratio to CSP infusion or standard care using a permuted block design with variable block sizes of 4 and 6. Predefined randomization assignment envelopes will be maintained within easy access in the ED. Randomization will be performed by a member of the study team. By tearing open the consecutively numbered envelope and retrieving the randomization card, the arm assignment will be provided in real time at the individual patient level. Trauma attending and ED physicians will not be masked to treatment assignment as the study intervention is a blood product and full traceability is required. Arm assignment will be concealed to all outcome assessors.

IV. Outcomes

Primary Outcome**:** The primary outcome for the pilot trial is feasibility. Secondary performance and feasibility outcomes will include 1) the proportion of eligible patients that can be randomized, 2) the proportion of eligible patients who are enrolled in the trial, 3) proportion of enrolled patients which adherence to the study protocol, and 4) proportion of enrolled patients who complete study follow-up.

Secondary Outcomes**:** *Our principal secondary clinical outcome for the trial will be 24 hour mortality.* Additional secondary outcomes for the proposal will include 3-hour mortality, in hospital mortality, 30-day mortality, death from hemorrhage, blood and blood component transfusion requirements in the initial 24 hours, incidence of acute respiratory distress syndrome (ARDS), time to hemostasis, incidence of coagulopathy by TEG, incidence of allergic/transfusion reaction, incidence of transfusion related acute lung injury (TRALI),measurements of platelet hemostatic function, and incidence of thromboembolic events.

Secondary Outcome Definitions:

3-hour, 24-hour, In-hospital mortality and 30-day mortality: 3-hour, 24-hour, in hospital mortality and 30-day mortality will be recorded from the time of randomization. *We will focus on 24 hour for our principal clinical outcome for the study.* Over the first 24 hours we will document and record the time of death in hours, while after the 24-hour time period, we will document and record the time of death in days from arrival. We suspect that patients in hemorrhagic shock will have a significant percentage of mortality occurring in the first 24-hour period.

Mortality from hemorrhage: Cause of death will be adjudicated by a site investigator who is blinded to the arm of the trial.

24-hour blood and blood component transfusion requirements: 24-hour blood and blood component transfusion requirements will be determined by recording the type of product, the number of units transfused, and the time of transfusion from the time of

randomization and the intervention completed. Any initiation of blood transfusion will be considered completed.

Acute Respiratory Distress Syndrome (ARDS): The Berlin definition for mild ARDS (PaO_2/FIO_2, ≤ 300 mm Hg + timing, imaging and origin criteria) will be utilized as a threshold value to determine the incidence of ARDS and will be further stratified into Moderate (PaO_2/FIO_2, ≤ 200 mm Hg) and Severe (PaO_2/FIO_2, ≤ 100 mm Hg).[23]

Coagulation parameters: Data will be obtained from clinical labs drawn during the first 60 minutes for PT, INR and point of care rapid-TEG analysis. Data from these measurements will also be obtained from clinical draws performed as close to 24 hours from the time of arrival as feasible.

Time to hemostasis: The time to hemostasis outcome variable will be determined by the by the ability to reach a nadir transfusion requirement of 1 unit of red blood cells in a 60-minute time period in the first 4 hours following arrival. Surgeon directed time to hemostasis may also be collected during the case. In the absence of the ability to obtain hemostasis by either of these criteria within the first 4 hours, the patient will be designated a 'non-hemostasis' patient.

Allergic/Transfusion reaction: Any transfusion complication in the ED and OR/IR setting will be monitored. As the intervention is specific to the early phase of care setting and since transfusion complications are temporally related to the specific transfusion, all transfusion related complications will be assessed during the initial 24 hours from arrival and recorded.

Transfusion Related Acute Lung Injury (TRALI): TRALI will be defined as the occurrence of ARDS (mild; PaO_2/FIO_2, ≤ 300 mm Hg) that occurs within 6 hours of transfusion of a blood product. There may be multiple blood products transfused to the patient including FDP, PRBC's, plasma, platelet during the early resuscitation period. The causal factor that results in TRALI may be unable to be determined but will be recorded.[24,25]

Platelet hemostatic function: We will assess platelet count utilizing standard hematology testing technique and platelet hemostatic function utilizing the TEG parameter Maximal Amplitude (MA).

Thromboembolic events: Pulmonary embolism, venous thrombosis, or arterial thrombosis that occurs during the primary admission hospital stay will be documented for all enrolled patients. Radiographic confirmation via CT imaging, transthoracic or trans-esophageal echo, or ventilation/perfusion scanning will be required. Presumed or clinical suspicion for an embolic event that is unable to be verified radiographically will also be documented.

Classification of Mortality**:** Classification of the underlying mechanisms responsible for mortality are essential to appropriately characterize regional variation and preventable morbidity

and mortality. Classification of mortality outcomes will be assigned at the level of the enrolling institution by the respective Site Investigator. A predefined list of mortality classifications will be provided and adjudicated upon at the site level and will include
1) Hemorrhage/Exsanguination, 2) TBI/herniation, 3) Multisystem Organ Failure, 4) Sepsis, 5) ARDS, 6) Coagulopathy, 7) Cardiac Arrest with 1-6, 8) Pulmonary Embolism, 9) Withdrawal of Care as well as other pertinent causes of injury related death.

Predefined Subgroups**:** Predefined subset analyses will be performed looking at 1) Patients who ultimately did or did not required in-hospital blood transfusion; 2) Patients with and without significant traumatic brain injury (Head abbreviated injury score- AIS >2); 3) Patients arrived from the scene of injury versus those brought from a referral hospital; 4) Patients who ultimately did or did not require massive transfusion (≥ 10 units blood in first 24hrs). 5) CSPs with shelf time of 1 to 7 days as compared to 8 to 14 days. It is recognized that the study is not appropriately powered for these subgroup comparisons and the results and conclusions formulated from these subgroup analyses will be considered exploratory in nature and will not be used as a basis for treatment recommendations.

V. Screening and Enrollment

Subjects will be identified prospectively in the ED by research personnel that are trained and familiar with the inclusion and exclusion criteria. Those patients who meet all inclusion and no exclusion criteria will be randomized to CSPs or standard of care based upon the predetermined randomization assignment. Clinically obtained laboratory measures will be utilized for our secondary outcomes of interest, including point of care rapid or conventional thromboelastography (TEG) performed for coagulation parameter measurements within 60 minutes of patient arrival and at 24 hours when feasible and with flexible time range +/-12hours.

VI. Statistical Analysis Plan

The analysis will begin by describing the baseline demographic and clinical characteristics of the overall population and then stratified by treatment arm to compare those who receive CSP and those who receive standard care. For discrete variables, proportions will be generated, and a chi-square test will be used to test for differences between the proportions. For continuous characteristics, means (medians) and standard deviations (interquartile ranges) will be calculated and t-tests (Wilcoxon) will be used to compare the means (distributions) between treatment arms.

Eligibility, Enrollment, and Subject Accrual: The feasibility of enrollment will be evaluated by determining 1) the proportion of eligible patients that can be randomized and 2) the proportion of eligible patients who are enrolled in the trial, 3) proportion of enrolled patients which adherence to the study protocol, and 4) proportion of enrolled patients who complete study follow-up. These proportions will be estimated directly as the observed ratio of numbers of patients, and 95% confidence intervals will be calculated to understand the likely range of values for a larger study with a comparable research protocol and population. The reasons why patients are not enrolled including frequencies of individual exclusions and the proportion of patients declining

participation or not able to be randomized will be described. Rate of subjects' accrual per month with 95% C.I. will be calculated.

Analysis for Trial Clinical Outcomes: For the primary trial outcome, an indicator of death within 24 hours will be generated for each participant. A two-sided z-test for proportions will be used to compare the proportions between the treatment arms. A logistics regression model will then be used to assess the independent impact of CSP on 24 hour survival after controlling for potential confounding effects of baseline characteristics which reveal imbalance between treatment groups. The same analytic approach will be used for other binary outcomes (e.g., mortality from hemorrhage).

For continuous outcomes (e.g., number of units transfused), a t-test or Wilcoxon test will be used to compare the number of units transfused between the two treatment group. An analysis of covariance model will be used to estimate the independent effect of treatment after controlling for the potential confounding effects of baseline characteristics which reveal imbalance between treatment groups

For time to event outcomes (e.g., time to hemostasis), Kaplan-Meier curves will be generated for each treatment group and a log-rank test will be used to compare the distribution of the cumulative proportion. Cox proportional hazard regression analyses will then be used to estimate the independent effect of treatment after controlling for the potential confounding effects of baseline characteristics which reveal imbalance between treatment groups.

Analyses to test for the homogeneity of the treatment effect will be carried out for the pre-defined subgroups. Regression models appropriate for the outcome variable (e.g., logistic regression for binary outcome variables) will be used to test for the homogeneity of the treatment effect. Main effects will be included in the model for treatment, the indicator of the subgroup and the two-way interaction between treatment and subgroup. If a statistically significant interaction is observed, we will reject the null hypothesis of a homogenous treatment effect.

Secondary analyses will be conducted to assess aim 3. These analyses will be carried out among those who are randomly assigned to the CSP group and the impact of the age of the CSP on outcomes will be evaluated. Since the secondary sample will not be randomly assigned, it will be important to adjust for potential confounding effects. A propensity score will be generated as an indicator of the age of the CSP (<= 7 days vs. > 7 days). Multivariable regression models will be used to assess the independent relationship of age of the CSP on outcome. The model type will vary based on the outcome (e.g., logistic regression for binary variables). Each model will include a fixed main effect for the indicator of the age of the CSP as well as an inverse probability weight for the propensity of getting CSP <= 7 days of age.

A prespecified analysis of the pilot data will include a stratified analysis in those patients who did or did not receive whole blood. An analysis will also be performed controlling for important confounders as well as whole blood transfusion and testing for differential treatment effect between those that received whole blood and those that did not. A dose response analysis will similarly be performed to characterize the number of transfusions of cold stored platelets a

patient receives and associations with primary and secondary outcomes (cold stored platelet transfusion and or whole blood transfusion which includes cold stored platelets)

Sample Size Justification and Power Analysis (n=200): For the enrollment, adherence and event rates needed for planning and feasibility analyses, we calculated the two-sided 95% CI for proportions ranging from 0.7 to 0.9. For example, a sample size of 200 produces a two-sided 95% CI of 0.85 to 0.94 when the sample proportion is 0.90. When the sample proportion is .70, the two-sided CI is 0.63 to 0.76. These confidence intervals are then repeated within the treatment arm.

Sample Size	Width	Proportion (P)	Lower Limit	Upper Limit
Full Sample				
200	0.13	0.700	0.63	0.76
200	0.11	0.800	0.73	0.85
200	0.09	0.900	0.85	0.94
One Treatment Arm				
100	0.19	0.700	0.60	0.79
100	0.17	0.800	0.71	0.87
100	0.13	0.900	0.82	0.95

For the primary clinical outcome of 24-hour mortality, based on a 2x2 (treatment x 24-hour mortality) there is 80% power to detect an effect size of 0.1981 (which translates into the ability to detect a 14.2% difference from a mortality rate of 23% in the control group) assuming a type I error rate of 0.05, a two-sided alternative hypothesis, 1 degrees of freedom, and a sample size of 100 participants per treatment group. After adjusting for the Bonferroni correction associated with the interim analysis, the type I error will decrease to 0.025 and the effect size will increase to 0.2180 which translates into 80% power to detect a statistically significant difference between the two groups, assuming a true difference of 15.3%.

Randomization of Ineligible Subjects: It is anticipated that there will be a small proportion of patients enrolled who receive CSPs or standard care that in retrospect will not have met the entry criteria and are thus ineligible. In this circumstance, patients will be analyzed according to the group to which they were randomized. Subgroup analyses based on eligibility criteria will be performed if the number of patients so affected is large. However, based on the relatively limited inclusion and exclusion criteria it is anticipated that the frequency of this event will be low.

Non-adherence: In some circumstances, patients may receive standard care instead of the CSPs intervention when randomized to CSPs. Non-adherence is most likely to occur in the case of the patient who requires urgent neurosurgical intervention and despite CSPs being available, are not used. Fortunately, this event is relatively rare. In keeping with the intention-to-treat analytic design, these patients will be analyzed with the group to which they were randomized.

Interim Analyses**:** The primary safety outcome will be 24-hour mortality. The analyses described earlier will be carried out twice, once when half of the sample has completed the assessment of the endpoint and once when the complete sample has completed the assessment of

the endpoint. To control for overall type I error a Bonferonni correction will be employed, allocating 0.025 of the type I error to each analysis.

Data Sources**:** Data will be collected prospectively as patient care progresses. This will include a review of the emergency medical patient care report(s), Emergency Department and electronic/ paper hospital records.

> In-Hospital Resuscitation Elements**:** Demographics, injury characteristics, ED vitals, ED interventions (chest tubes, intubation), injury severity, operative interventions and timing of interventions, injury severity score, ICU days, ventilator days, length of stay.

Data Entry**:** The DCC will create web-based HTML forms to collect necessary information from all participating sites. Web entry forms will have dynamic features such as edit and data type checks. Details and clarification about data items will be provided using pop-up windows. Data encryption and authentication methods will be used. Additional features will be built into the web entry forms including: forms transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms. The subjects will be identified by a study number only. All clinical interventions will become part of the patient's medical records including platelet transfusion. All hard copy source documentation will be kept in a secured, locked cabinet in the site's research coordinator's office. All study documents will be maintained in a secure location for the time frame designated by each participating site's requirements. The electronic data will be entered and maintained on a password protected SSL website designed for this trial.

The data entered for the CriSP-HS trial will be maintained by the DCC on a relational database. The database would be housed in a virtual environment so in the event of a hardware failure it would migrate to a new host. The data will be backed on a regular schedule with full transaction log files in use and copies of the data will be stored offsite with a secure service. In addition to the data server, the production web server will also be backed up routinely and as a virtual machine can be transitioned to different hardware automatically in case of hardware failure. All Servers are behind an enterprise firewall and access has to be granted through the firewall even within the University Network.

Database Management**:** A two-tiered database structure will be created. A front-end database will serve the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred on a regular schedule to a data repository that can be used by statistical software packages. These datasets will be the basis for data queries, analyses and monitoring reports. Various versions of this database will be kept as needed, e.g. for quarterly performance reports. Access to data will be limited to those who need access to perform their tasks. The database management system is able to manage large quantities of data, to merge data from multiple databases as required, to handle complex and possibly changing relationships, and to produce analysis datasets that can be imported into a variety of statistical analysis packages.

Surveillance for Outcomes and Data Elements**:** Data will be collected prospectively as patient care progresses. This will include a review of the emergency medical patient care report(s), Emergency Department and electronic/ paper hospital records.

> In-Hospital Data: Demographics, shock severity (base deficit, lactate), injury characteristics, ED vitals, ED interventions (chest tubes, intubation), injury severity, operative interventions and timing of interventions, injury severity score, ICU days, ventilator days, length of stay, multiple organ dysfunction scores (daily), nosocomial infectious outcomes, blood gas results, cxray reads, transfusion of blood and blood components, resuscitation requirements, all primary and secondary outcomes will be recorded.

VII. Clinical Coordinating Center (CCC)

Clinical Coordination specific for the CriSP-HS study will be performed by MACRO (Multidisciplinary Acute Care Research Organization) and their dedicated research teams at the University of Pittsburgh, including all regulatory requirements, provider and coordinator training and monitoring.

VIII. Data Coordinating Center (DCC)

Data Coordination specific for the CriSP-HS study will be performed by the DCC and led by Dr. Wisniewski at the Graduate School of Public Health at the University of Pittsburgh. The DCC will coordinate all data collection and entry, management, security and confidentiality, data archiving, quality control and electronic medical record biomedical informatics as needed, as well as plan, coordinate and assist with all statistical analyses.

IX. Human Subjects

We anticipate that this study will be conducted under the federal provisions governing Exception from the Requirement for Informed Consent for Emergency Research, including community consultation, public notification, as well as notification of patients or their legally-authorized representative as soon as feasible after enrollment. The latter shall include provision of an opportunity to opt out from ongoing participation that will be given through oral and written communication.

Due to the nature of the population and the very limited therapeutic window, we anticipate that prospective informed consent will not be feasible. The patient and/or family member or LAR will be informed at the earliest feasible opportunity of the subject's inclusion in the clinical trial and will be asked to provide consent for continuing participation. The investigators will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review if requested. The investigators will utilize available information and resources, such as social workers or social work notes, to try to locate the patient's legally authorized representative. If that search is unsuccessful, and the subject remains incapacitated, a notification letter will be sent to the subject's authorized representative

explaining the study and providing contact information for answering questions. The letter will be sent via trackable means and the addressee and date of mailing will be kept. If the subject becomes competent prior to discharge, then s/he will be approached for notification of enrollment and continued informed consent. At any circumstance a subject or their legally authorized representative will have an opportunity to opt out of ongoing participation without penalty or loss of benefits. If the subject dies before notification and consent can be obtained, a letter notification will be sent to the subject's family member to inform them that the subject was enrolled in this study.

Community consultation as determined by the central IRB will be undertaken prior to final IRB approval. We will utilize a central IRB at the University of Pittsburgh. Since the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate. Public notification and community consultation will be performed as directed by the central IRB and may include such methods as surveys of the proposed study community, targeted small group meetings or consultation with community leaders. Due to ongoing participation in numerous multicenter research studies involving emergency research, our institution and the other participating institutions have significant experience with community consultation and notification practices.

Study risks and benefits: Risks associated with blood component transfusion include infection, allergic reaction, fever, and respiratory distress. Additional risks associated with platelet transfusion include bacterial contamination, platelet alloimmunization, and hemolysis. Due to the higher activation in CSP as compared to RTP, there is a potential for increased risk of thrombotic complications. A detailed list of risks associated with the transfusion of platelets is included in the Investigator Brochure.

Regardless of arm, we anticipate that enrolled subjects will benefit from increased monitoring of primary and secondary outcomes, with particular focus on coagulopathy due to the focus of the trial.

Institutional Review Board: A central IRB will be utilized at the University of Pittsburgh for the regulatory needs of studies. All current LITES Network sites have IRBs which have experience and engagement with central IRB procedures.

Training and Participating Site Coordination**:** As the clinical coordinating center for the trial, the University of Pittsburgh (MACRO) at the University of Pittsburgh will be collaboratively responsible for all research coordinator training, provider training and sample collection and storage. Research coordinators, providers and associated staff will be trained during the months prior to the trial start date regarding the scientific basis for the study, specific inclusion and exclusion criteria, sample collection and processing, study procedures and SOPs, and rapid TEG performance. Training verification and retraining will occur if new staff is hired at individual participating sites.

X. Safety Monitoring

Adverse Event and Non-compliance definitions

a. Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

b. Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

c. Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

d. Reasonable possibility. For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

e. Unexpected adverse event/reaction refers to an event/reaction that is not consistent with the risk information described in the general investigational plan or elsewhere in the IND application.

f. Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

f. Serious, suspected adverse reaction. A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site principal investigator) or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

g. *Reportable non-compliance* refers to a failure on the part of the investigator or study team member to follow the terms of the IRB approved protocol or abide by applicable laws or regulations, that adversely affect the rights and welfare of subjects or significantly compromises the quality of the research data. Incidents of non-compliance on the part of the subject are not considered reportable.

h. Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) refers to any accident, experience, or outcome that meets the following criteria: unexpected in terms of nature, severity or frequency; related, or possibly related, to a subject's participation in research; and places subjects or others at greater risk of harm (including physical, economic, or social) than was previously known or recognized.

Assessing and Reporting Adverse Events (AEs) and Non-compliance: Adverse events will be reviewed by the study sites and assessed for relationship to the study intervention. Investigators and study team will determine if any related adverse events occur during the period from enrollment through hospital discharge. If reportable adverse events occur, they will be recorded on the adverse event case report form in the electronic data capture system, which will be submitted to the Coordinating Center. All reported adverse events will be classified by: a) Severity (fatal or life-threatening, serious, or non-serious); and b) Expected vs. Unexpected. An

event will be determined to be unexpected if it is not consistent with the risks identified in the Investigator's Brochure or with the information provided in the general investigational plan or elsewhere in the IND application. Please refer to the table below for timelines for reporting.

This study population is expected to have a large number of serious adverse events, including death from trauma related injuries. Expected adverse events that are related or possibly related to the intervention will be documented and reviewed for changes in nature, severity, or frequency across the study population.

Organization	Unexpected, fatal or life-threatening, suspected adverse reactions	Unexpected, serious, suspected adverse reactions	Expected adverse reactions	Reportable non-compliance	UPIRTSO
IRB	24 hours	10 working days	No reporting	10 working days	10 working days
FDA	7 calendar days	15 calendar days	No reporting	No requirement	No requirement
Dept of Defense	30 calendar days	30 calendar days	No reporting	30 calendar days**	30 calendar days*
DSMB	24 hours	7 calendar days	At next meeting (every 6 months)	At next meeting (every 6 months)	14 days*

*reported based on IRB determination that event is UPIRTSO
**reported based on IRB determination that non-compliance is serious or continuing

Data Safety Monitoring Board (DSMB)**:** A Data and Safety Monitoring Board (DSMB) will be created to review this study and provide recommendations re. study continuation to the IND Sponsor. After initial approval and at periodic intervals (to be determined by the committee) during the course of the study, the DSMB responsibilities are to:

a. Review the research protocol, informed consent documents and plans for data and safety monitoring;
b. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect study outcome;
c. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the

participants or the ethics of the study;
d. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the IND Sponsor or study site Investigators;
e. Protect the safety of the study participants;
f. Report on the safety and progress of the study;
g. Make recommendations to the IND Sponsor, and if required, to the FDA concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;
h. Monitor the confidentiality of the study data and the results of monitoring;
i. Assist the IND Sponsor by commenting on any problems with study conduct, enrollment, sample size and/or data collection.
j. The DSMB will include experts in emergency medicine, surgery (trauma/critical medicine), hematology, bioethics and biostatistics. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.
k. The University of Pittsburgh Office of Clinical Research, Health Sciences will provide the logistical management and support of the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.
l. The first meeting will take place before initiation of the study to discuss the protocol, approve the commencement of the study, and to establish guidelines to monitor the study. The follow-up meeting frequency of the DSMB will be determined during the first meeting. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of patient safety arise.

XI. Quality Control, Assurance and Confidentiality

Protocol Compliance: The participating study site Investigators will not deviate from the protocol for any reason without prior written approval from the IRB except in the event of the safety of the research subject. In that event, the study site Investigator will notify the IND Sponsor and reviewing IRB immediately, if possible, and request approval of the protocol deviation, or, if prospective IND Sponsor and IRB approval is not possible, the study site Investigator will notify the IND Sponsor and reviewing IRB promptly following the respective protocol deviation. The study site Investigator will inform the reviewing IRB of all protocol deviations and unanticipated events involving risks to the research subjects and others, and will obtain prospective IRB approval for all proposed protocol changes. Persistent or serious noncompliance may result in termination of the study site's participation in the research study.

Protocol Deviations: Due to the relative focused inclusion criteria and the short intervention period, we expect few protocol deviations as compared to other large multicenter trials. If monitoring reports demonstrate evidence of continuing protocol deviations, we will analyze them to determine if they are site specific or common across the study. We will note if specific inclusion or exclusion criteria are being misinterpreted, if a certain time point in testing is being omitted, or if a common set of data elements are missing. If the deviations are site specific, retraining will be done at the site. If the problems are study wide, we will discuss them with the

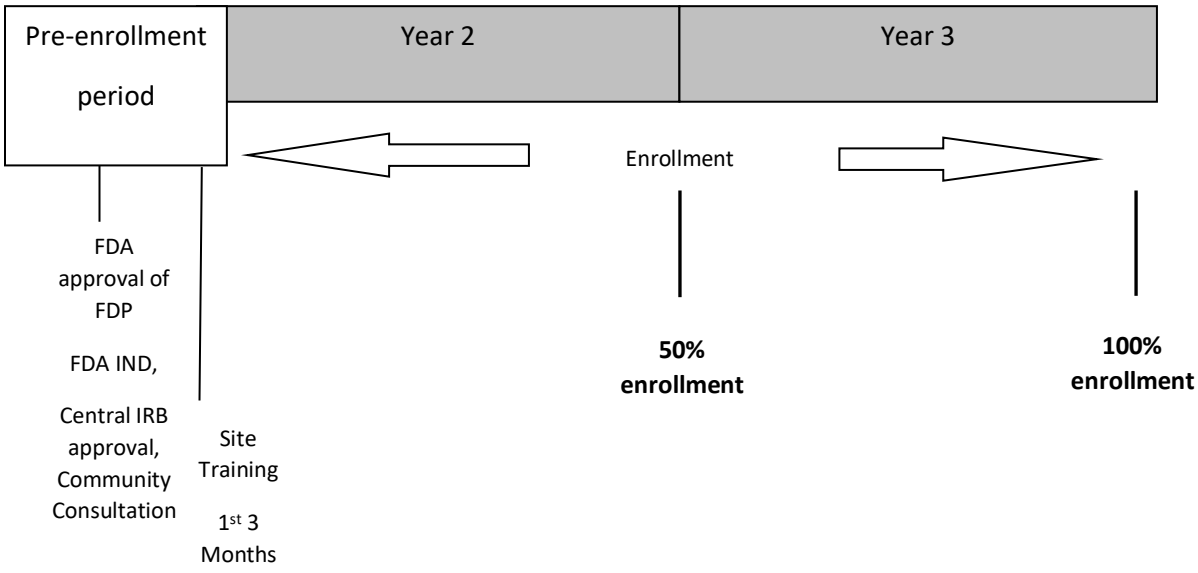
other investigators, the DOD and the FDA to see if the protocol needs to be amended or recruitment put on hold.

Privacy and Confidentiality: The study site Investigator's and members of their research team will make reasonable effort to ensure the research subjects' confidentiality. Subject name and other identifiable information will be kept in a secure, locked, limited access area.

Investigator Responsibilities:

The study site Investigators will agree to implement the IRB approved protocol and conduct the study in accordance with Section 9 (Commitments) of Form FDA 1572, 21 CFR Part 312, Subpart D, and the ICH GCP Guidelines (E6, Section 5) as well as all applicable national, state and local laws. The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Time Table:



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XIII. Appendix I Requirements for Exception From Consent For Emergency Research

We have outlined below each criterion stipulated in the regulations for this exception and how our study design applies to these criteria.

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

The proposed trial is a randomized trial comparing the use of cold stored platelets versus standard of care in patients in hemorrhagic shock following injury requiring operative management. These patients are in a life-threatening situation with a mortality before discharge approaching 30-40% despite all efforts. The standard of care for management of these patients generally includes component resuscitation. Importantly, prior studies have demonstrated that injured patients who require large volume blood transfusion have improved survival if transfusion of high or equal ratios of plasma and platelets to blood occurs. Evidence suggests that early blood component transfusion may reduce overall blood transfusion requirements and that addressing the coagulopathy which occurs early after injury improves outcome.

(2) Obtaining informed consent is not feasible because:
i. The subjects will not be able to give their informed consent as a result of their medical condition;
ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

The study intervention needs to be administered quickly after arrival to the trauma center (see discussion of therapeutic window below). In this chaotic initial treatment phase, the hemorrhagic shock patient is unable to provide consent for study enrollment, as they are commonly unconscious or in extremis, and legal next-of-kin are often not immediately available, nor is it practical for the hospital provider to explain the study and receive consent while caring for the patient emergently. Since we are studying patients with hemorrhagic shock following injury, there is no way to prospectively identify individuals who are likely to become eligible for this trial.

(3) 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;
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
iii. 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.

(i) As defined, these patients are injured and in hemorrhagic shock and are facing a potentially life-threatening situation that requires immediate intervention.
(ii) Previous animal and human studies suggest the potential for a direct benefit to individual patients who are in hemorrhagic shock.
(iii) Platelets have been shown to provide a survival benefit for massive transfusion. The current protocol will allow early access to these benefits as compared to current standard care. Whole blood has been evaluated in military and civilian settings, which contains cold stored platelets

(4) The clinical investigation could not practicably be carried out without the waiver.
This study could not be conducted without the waiver of consent due to the need to initiate the intervention quickly upon arrival for hemorrhagic shock patients at significant risk of mortality.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

Patients in hemorrhagic shock following injury have been shown to develop progressive hypothermia, coagulopathy and acidosis leading to further recalcitrant hemorrhage and multisystem organ failure and death. It has been shown that an increased mortality of 1% is demonstrated for every 3 minutes of delay to the operating room a patient has. In a recent study from PROPPR, every 1 min delay in blood products getting to the patients is associated with a 5% higher mortality. These data demonstrate the potential therapeutic window in 1-3 minutes, which is an insufficient amount of time to contact legal representatives and conduct an informed consent discussion. We will make every effort to contact legal representatives as soon as feasible to notify them that the patient was enrolled in a randomized trial and will attempt to obtain their informed consent to continue participation. A summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period, then he/she will be approached by research personnel for notification of enrollment and continuing consent.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

All procedures and consent forms will be approved by the Single Institutional Review Board (sIRB) of the study prior to the onset of the trial.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;
ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
v. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(i) Community consultation as outlined by the sIRB will be undertaken prior to IRB approval. Since the population eligible for enrollment includes all citizens in the study region it will not be possible to target any particular small group. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate. Public notification and community consultation will be performed as directed by the sIRB and may include such methods as using online surveys of the proposed study community, targeted small group meetings or consultation with community leaders. Our institution has significant experience with community consultation and notification practices.
(ii) & (iii) Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the investigators. These will include plans for the study including potential risks and benefits and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements may also be placed in local papers describing the study.
(iv) The Data Safety Monitoring Board will function as an independent data monitoring committee who will exercise oversight of the study. An independent Research Monitor will also be appointed per Department of Defense requirement.
(v) We expect that all patients who meet the enrollment criteria will be unconscious or in critical state that does not allow appropriate consent to occur. Any delay in medical care that would be required for the care provider to attempt to obtain consent from the patient's legal guardian would be life threatening. Thus, it will not be feasible to attempt to obtain informed consent during the initial therapeutic window. Requiring consent to review a hospital chart to determine the presence or absence of serious adverse events is likely to be associated with a biased estimate of the safety and efficacy of the intervention. Therefore, we will use exception from consent for emergency research which includes public notification, community consultation, patient notification of enrollment, and provision of an opportunity to opt out from ongoing participation.