Linking Investigations in Trauma and Emergency Services

Cold Stored Platelet Early Intervention – Traumatic Brain Injury (TBI) (CriSP-TBI) trial Task Order 0004

Protocol number: STUDY20070044

Version number and date: Version 12 - 02/08/2023

Phase of clinical investigation
Phase II Clinical Investigation

IND number: Investigational drug:
IND application number #25180
Cold Stored Platelets

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Principal-Investigator: David Okonkwo, MD, PhD

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Protocol Synopsis

Protocol Title:	Cold Stored Platelet Early Intervention - TBI (CriSP-TBI) Trial
Protocol Number:	STUDY20070044
NCT Number:	NCT04726410
Version # and Date:	Version 12 dated 02/08/2023
Investigational Drug:	Cold Stored Platelets (CSP)
Clinical Phase	Phase II
Funding Agency	Department of Defense
IND Sponsor:	Jason L Sperry, MD, MPH
Principal Investigator:	David Okonkwo, MD, PhD
Research Facility	UPMC Presbyterian Hospital
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 TBI requiring platelet transfusion. **AIM#2:** Determine whether early cold stored platelet infusion compared to standard platelet transfusion results in improved clinical outcomes and hemostatic function in patients with traumatic brain injury requiring platelet transfusion. **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 TBI on antiplatelet therapy.
Study Design:	Open label, single center, randomized trial designed to determine the feasibility, efficacy and safety of urgent release cold stored platelets in blunt injured patients with traumatic brain injury requiring platelet transfusion.
Planned Sample Size:	100 subjects with TBI
Planned Study Time:	3-year study with 2 years of enrollment
Major Inclusion Criteria:	Patients with traumatic brain injury, defined by presence of potential progressive intracranial injury on CT scan imaging, at significant risk for urgent neurosurgical procedure as determined by neurosurgical evaluation, who meet at least one of the following: a) History or indication of pre-injury oral antiplatelet agent use b) Need for platelet transfusion per standard practice
Major Exclusion Criteria:	**1.** Wearing NO CriSP opt out bracelet **2.** Hypotension in ED (SBP< 90 mmHg)

	3. Age > 89 or < 18 years of age **4.** Penetrating injury **5.** Prisoner **6.** Pregnancy **7.** Going to operating room for non-neurosurgical intervention in first 60 minutes **8.** Platelet transfusion contraindicated per care team (for example, recent vascular stent, embolic stroke, intracranial and/or vascular lesions) **9.** Objection to study voiced by participant or family member in Emergency Department **10.** Currently on therapeutic anticoagulant in addition to aspirin and/or clopidogrel (e.g. warfarin, direct-acting oral anticoagulants)
Primary Endpoint:	Feasibility
Secondary Endpoints:	• 24-hour mortality • GOSE at 6 months

Specific Aims

Platelet transfusion is commonly provided early after injury in patients with traumatic brain injury (TBI) to reverse antiplatelet medications (aspirin, Plavix). Taking antiplatelet medications potentially worsens intra-cranial hemorrhage and outcomes following TBI. Importantly, other antiplatelet medications such as NSAIDs have also been shown to inhibit platelet aggregation and compromise coagulation at doses commonly taken by warfighters.[1] Whether current standard care room temperature (RT) platelet transfusion adequately reverses platelet inhibition and improves outcomes following traumatic brain injury remains poorly characterized. Cold stored platelets may provide better hemostatic correction and improve outcomes in patients with TBI requiring platelet transfusion.

Platelet use in far forward environments are not available due to logistical storage and shelf-life requirements. Cold-stored platelets can be refrigerated like 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.[2-6] For patients with brain injury, 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 TBI (CriSP-TBI) pilot trial are to determine the feasibility, efficacy and safety of urgent release cold stored platelets in patients with traumatic brain injury requiring platelet transfusion.

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 TBI requiring platelet transfusion.
AIM#2: Determine whether early cold stored platelet transfusion compared to standard platelet transfusion results in improved hemostatic function and clinical outcomes in patients with traumatic brain injury requiring platelet transfusion.

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 TBI on antiplatelet therapy.

Hypothesis for clinical outcomes: Early infusion of cold stored platelets as compared to standard platelet transfusion will result in improved 6 month Extended Glasgow Outcome Scale (GOS-E), lower 24 hour and in-hospital mortality, a lower need for craniotomy/craniectomy, lower need for ICP monitoring, a lower rate of TBI progression, improved hemostatic function, reversal of platelet inhibition and a similar rate of allergic/transfusion reactions and incidence of transfusion related acute lung injury in patients with TBI requiring platelet transfusion.

Background and Significance

Platelet transfusion is commonly provided to patients with moderate or severe TBI who are on antiplatelet medications. Evidence suggests that patients on antiplatelet medications may have worse outcomes following TBI.[7-10] Current literature has not demonstrated major outcome improvements in those patients who receive platelet transfusion.[11,12] This lack of significant benefit may be due to insufficient dosing or due to the poor hemostatic function of standard care room temperature platelets. Studying the potential benefits of Cold Stored Platelet transfusion in the TBI population will provide needed direct comparison of room temperature and cold stored platelet transfusion which is unable to occur in patients with hemorrhagic shock, who may require large volumes of red blood cells and plasma concomitantly with platelet transfusion.

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 TBI patients requiring platelet transfusion. 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.

Study Design/Setting

The current proposed pilot study will be a 3-year, single center, open label, randomized trial utilizing a level-1 trauma center at the University of Pittsburgh and will randomize approximately 100 patients with TBI.

Study Population**:** Traumatic brain injured patients with a non-penetrating injury requiring platelet transfusion.

Inclusion Criteria:

Patients with traumatic brain injury, defined by presence of potential progressive intracranial injury on CT scan imaging, at significant risk for urgent neurosurgical procedure as determined by neurosurgical evaluation, who meet at least one of the following:

a) History or indication of pre-injury antiplatelet agent use
b) Need for platelet transfusion per standard practice

Exclusion Criteria:

1. Wearing NO CriSP opt out bracelet
2. Hypotension in ED (SBP< 90 mmHg)
3. Age > 89 or < 18 years of age
4. Penetrating injury
5. Prisoner
6. Pregnancy
7. Going to operating room for non-neurosurgical intervention in first 60 minutes
8. Platelet transfusion contraindicated per care team (for example, recent vascular stent, embolic stroke, intracranial and/or vascular lesions)
9. Objection to study voiced by participant or family member in Emergency Department
10. Currently on therapeutic anticoagulant in addition to aspirin and/or clopidogrel (e.g. warfarin, direct-acting oral anticoagulants)

Screening and enrollment: Participants will be identified prospectively, within the 2-hour period after CT scan in the ED, by research personnel that are trained and familiar with the inclusion and exclusion criteria. An additional CT scan may be performed as standard care at UPMC Presbyterian for those participants being transferred to UPMC Presbyterian after the injury is identified at an outside facility. Those subjects who arrive more than 2 hours after initial scan at the outside hospital will still be considered for enrollment. Patients who meet all inclusion and no exclusion criteria will be randomized to CSPs or standard of care based upon the predetermined randomization assignment. Patients who meet all inclusion and no exclusion criteria will be randomized to CSPs or standard of care based upon the predetermined randomization assignment.

Capacity to provide informed consent will be assessed prior to randomization and will primarily be determined by Glasgow Coma Scale (GCS). Potential subjects with a GCS of less than 15 will be considered unable to consent. Potential subjects with a GCS of 15 will undergo a GOAT assessment, performed by a study investigator or neurosurgery CRC. A score of 74 or below will be considered unable to consent. For subjects that are determined to be unable to consent, assent will be obtained when applicable. The study team will also attempt to identify an appropriate LAR to provide prospective informed consent. If a LAR is identified within the 2-hour period after initial CT scan in the ED, this individual will be approached for proxy consent. If not, the patient will be enrolled under EFIC. If a potential subject has a GCS of 15 and scores 75 or above on the GOAT, we will presume s/he is capable of providing direct informed consent and will seek to obtain informed consent via a physician investigator.

VerifyNow Measurements: When feasible, VerifyNow-Aspirin and VerifyNow-P2Y12 measurements for patients with a history of aspirin and/or clopidogrel, respectively, may be performed prior to platelet transfusion and for response monitoring following initial platelet transfusion. However, need for platelet transfusion will be determined by neurosurgical and/or trauma surgery recommendations. VerifyNow measurements will only be obtained when feasible. Measurement cut points for determining platelet inhibition will follow manufacturer guidelines https://www.werfen.com/na/en/verifynow .

Study Intervention:

Study Intervention Arm**:** Patients randomized to the intervention arm will receive an early infusion of urgent release cold stored platelets (CSP) once the patient is determined to meet all inclusion and no exclusion criteria. When clinically feasible, patients will undergo VerifyNow Aspirin or P2Y12 testing following initial platelet transfusion. Those patients who have not increased their respective ARU or PRU measurements to levels consistent with no drug effect (ARU > 550; PRU > 220), or who have another clinical indication for additional platelet transfusion, may undergo a second CSP infusion.

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 including packed red blood cells, plasma, or whole blood per institutional standard care. The administration will be begun by clinical staff.

Standard Care Arm**:** Patients randomized to the standard care arm will receive room temperature (RT) platelet transfusion per standard care at the University of Pittsburgh once the patient meets all inclusion and no exclusion criteria. When clinically feasible, patients will undergo VerifyNow Aspirin or P2Y12 testing following initial platelet transfusion. Those patients who have not increased their respective ARU or PRU measurements to levels consistent with no drug effect (ARU > 550; PRU > 220), or who have another clinical indication for additional platelet transfusion, may undergo a second RT platelet infusion.

Randomization and Masking**:** Individual patients determined to meet 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. The arm assignment will be provided in real time at the individual patient level by accessing an electronic randomization system. Backup envelopes containing randomization assignments will be available by contacting the Data Coordinating Center should there be any issues or failure of the electronic randomization system. Trauma and Neurosurgical 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 performing the GOSE during follow-up.

In order to facilitate the early administration of platelets, randomization of eligible patients will occur within 2 hours of diagnosis of TBI via CT scan in the ED.

The study team may call the participant to check on their status after 30 days and again after 6 months. If the participant is discharged to another facility, they may be contacted at that facility for an update of their condition.

If we are unable to get in touch with the participant or with the facility they were discharged to, we will check survival status on a public access database using personal identifiers such as name, date of birth, and social security number.

Follow-up procedures: Galveston Orientation and Amnesia Test (GOAT): We will obtain the GOAT score prior to discharge and the calculated score per standard methods.[34] (Figure 1) GOAT is a 10-item questionnaire used to quickly assess post-traumatic amnesia following head injury. The GOAT is read orally to the patient and may be easily administered at the bedside. The total score accounts for orientation of person, place, and time, and recollection of events pre and post- injury. Cutoff scores are available to identify abnormal, borderline, and normal orientation and it will additionally determine if a participant is able to provide continuing participation consent after the process of EFIC.

Figure 1:

The Galveston Orientation and Amnesia Test (GOAT)

Question	Error score	Notes
What is your name?	/ 2	Must give both first name and surname.
When were you born?	/ 4	Must give day, month, and year.
Where do you live?	/ 4	Town is sufficient.
Where are you now?		
(a) City	/ 5	Must give actual town.
(b) Building	/ 5	Usually in hospital or rehab center. Actual name necessary.
When were you admitted to this hospital?	/ 5	Date.
How did you get here?	/ 5	Mode of transport.
What is the first event you can remember after the injury?	/ 5	Any plausible event is sufficient (record answer)
Can you give some detail?	/ 5	Must give relevant detail.
Can you describe the last event you can recall before the accident?	/ 5	Any plausible event is sufficient (record answer)
What time is it now?	/ 5	1 for each half-hour error, etc.
What day of the week is it?	/ 3	1 for each day error, etc.
What day of the month is it? (i.e. the date)	/ 5	1 for each day error, etc.
What is the month?	/ 15	5 for each month error, etc.
What is the year?	/ 30	10 for each year error.
Total Error:		
100 - total error		Can be a negative number.

76-100 = Normal
66-75 = Borderline
< 66 = Impaired

Extended Glasgow Outcome Scale (6 months-GOSE): The GOSE score will be obtained at 6 months (+/- 1month) by home survey or direct patient contact, whichever is feasible. For those participants who were unable to consent at discharge, the GOAT will be administered to assess their ability to provide direct consent, prior to the administration of the GOSE. When the assessment is done by phone, the verbal consent of participants who have regained the ability to consent will be obtained to allow the GOSE to be completed. The score can characterize 6-month functional status into 8 well defined categories as shown in (Figure 2).

Figure 2:

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD -
4	Upper severe disability	SD +
5	Lower moderate disability	MD -
6	Upper moderate disability	MD +
7	Lower good recovery	GR -
8	Upper good recovery	GR +

Study Drug/Intervention: Up to 2 cold stored apheresis units issued at the University of Pittsburgh will represent the CSP intervention. The volume of each unit will be approximately 200-300 mls and each will be stored in an FDA monitored approved refrigerator at 1-6 degrees Celsius for up to 14 days from preparation.

Please refer to the Investigator Brochure for additional details regarding CSP preparation, labeling, storage, dosing, and administration.

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.

Outcomes

Primary Outcome**:** The primary outcome for this pilot trial will be feasibility. Secondary performance and feasibility outcomes will include 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 principle secondary clinical outcome for the proposal will be 6-month Extended Glasgow Outcome Scale (GOS-E).* Additional secondary outcomes will include 24-hour mortality, in-hospital mortality, need for craniectomy/craniotomy, need for ICP monitoring, TBI progression based upon serial CT imaging in initial 24 hours, Galveston Orientation and Amnesia Test (GOAT score) at discharge, 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:

Extended Glasgow Outcome Scale (6 months-GOSE): The GOSE score will be obtained at 6 months +/- 1month by phone survey or direct patient contact, whichever is feasible. Patients will be consented for this contact outcome. The score can characterize 6-month functional status into 8 well defined categories.

24-hour and In-Hospital Mortality: 24-hour and in hospital mortality will be recorded from the time of arrival. 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.

TBI progression in 24 hours: Common Data Elements (CDE) for CT scan indicators of hemorrhage progression will be utilized.[13]
https://www.commondataelements.ninds.nih.gov/Traumatic%20Brain%20Injury

Galveston Orientation and Amnesia Test (GOAT): We will obtain the GOAT score prior to discharge and the calculated score per standard methods.[14] GOAT is a 10-item questionnaire used to quickly assess post-traumatic amnesia following head injury. The GOAT is read orally to the patient and may be easily administered at the bedside. The total score accounts for orientation of person, place, and time, and recollection of events pre and post- injury. Cutoff scores are available to identify abnormal, borderline, and normal orientation and it will additionally determine if a participant is able to provide continuing participation consent.

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, $\leq$ 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 PRBCs, plasma in addition to platelets during the early resuscitation period. The causal factor that results in TRALI may be unable to be determined but will be recorded.[15,16]

Platelet Hemostatic Function: Once randomized, blood sampling for platelet hemostatic function prior to platelet transfusion irrespective of arm assignment will be performed if clinically feasible. Following each platelet transfusion, further assessment of platelet hemostatic function may be performed (up to 2 times). Platelet hemostatic function will be assessed by TEG analysis and TEG with platelet mapping. Whole blood aggregometry and flow cytometry will be performed when feasible across both arms.

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.

Severity Stratification**:** TBI characteristics will be recorded and based upon CT imaging results (classification: subarachnoid, subdural, intracerebral hemorrhage, epidural, +/- shift, multifocal) and TBI severity will be characterized by presenting GCS, Abbreviated Injury Severity (AIS) coding and Rotterdam CT scores.

Predefined Subgroups**:** Predefined subset analyses for the TBI cohort will be performed looking at 1) patients who did or did not receive a craniectomy/craniotomy, 2) patients who did or did not require ICP monitoring, 3) patients arrived from the scene of injury versus those brought from a referral hospital; 4) patients with a pre-injury history of aspirin use as compared to clopidogrel use; 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.

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 Participant Accrual: The feasibility of enrollment will be evaluated by determining 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. 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 participants' accrual per month with 95% C.I. will be calculated.

Analysis for Clinical Outcomes**:** The principal secondary clinical outcome for the trial will be 6-month Extended Glasgow Outcome Scale (GOS-E). The null and alternative hypothesis of the study are

H0: There is no difference in the distribution of the GOS-E scores by treatment group
H1: There is a difference in the distribution of the GOS-E scores by treatment group

A two-sided Chi-square test will be used to compare the distribution of the GOS-E between the treatment arms. An ordinal polytomous regression model will then be used to assess the independent impact of CSP on GOS-E after controlling for potential confounding effects of baseline characteristics which reveal imbalance between treatment groups. The analytic approach for the secondary trial outcomes will vary based on the type of outcome. For binary outcomes, a two-sided Chi-square test for proportions will be used to compare the proportions between those receiving and not receiving CSP. A logistics regression model will then be used to assess the independent impact of CSP on the secondary trail outcomes while adjusting for baseline GCS. For time-to-event outcomes (e.g., time to death), 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. A Cox-proportional hazards regression model will be used to assess the independent impact of CSP on time to death after controlling for baseline GCS. For continuous outcomes a two-sided t-test for means will be used to compare the means between those receiving and not receiving CSP. An analysis of covariance model will be used to assess the independent effect of CSP. after controlling for baseline GCS .

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 stratified by the pre-defined subgroups. Estimate of the treatment effect (odds ratio) and 95% confidence interval will be generated for each model and displayed on a forest plot.

Secondary analyses will be conducted to assess the impact of age of the CSP on outcomes. 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 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.

Sample Size Justification and Power Analysis **(n=100):** For the enrollment, adherence and event rates needed for planning and feasibility analyses, we calculated the two-sided 95% CI for proportions ranging from 0.70 to 0.90. For example, a sample size of 100 produces a two-sided 95% CI of 0.82 to 0.95 when the sample proportion is 0.90. When the sample proportion is .70, the two-sided CI is 0.60 to 0.82. These confidence intervals are then repeated within the treatment arm.

Sample Size	**Width**	**Proportion (P)**	**Lower Limit**	**Upper Limit**
Full Sample				
100	0.19	0.700	0.60	0.82
100	0.17	0.800	0.71	0.87
100	0.13	0.900	0.82	0.95

One Treatment Arm				
50	0.27	0.700	0.55	0.82
50	0.24	0.800	0.66	0.90
50	0.19	0.900	0.78	0.97

For the principle secondary clinical outcome of the GOSE, based on a 2x8 (treatment x GOSE) there is 80% power to detect an effect size of 0.3788, assuming a type I error rate of 0.05, a two-sided alternative hypothesis, 7 degrees of freedom, and a sample size of 50 participants per treatment group.

Randomization of Ineligible Participants**:** 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.

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. 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.

Clinical Coordinating Center (CCC)

Clinical Coordination specific for the CriSP-TBI study will be performed by the LITES Network Clinical Coordinating Center at the University of Pittsburgh and Dr. Okonkwo's Neurosurgery research staff and their dedicated research teams at the University of Pittsburgh, including all regulatory requirements, provider and coordinator training and monitoring.

Data Coordinating Center (DCC)

Data Coordination specific for the CriSP-TBI 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 design data collection forms, build and maintain an electronic data management system, provide training and technical assistance for site-based data entry personnel, develop and implement quality control mechanisms (including in-person and remote monitoring), and produce reports. The DCC will also plan, coordinate, and carry out statistical analyses and make the datasets available for public use after the trial is completed.

Data Management

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.

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

> Prehospital elements: Mechanism of injury, prehospital vital signs including lowest GCS, lowest systolic blood pressure, highest heart rate, need for intubation/advanced airway, transported from scene, transported from referral hospital, ground transport, air medical transport.
>
> In-Hospital Data: Demographics, shock severity (base deficit, lactate), injury characteristics, GCS and pupil exam, 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, x-ray reads, transfusion of blood and blood components, resuscitation requirements, all primary and secondary outcomes will be recorded.

Data Entry**:** The DCC will create an electronic data management system that will include a password-protected SSL website for data entry with built-in dynamic features such as data encryption, user authentication, range and data type checks, real time reports, data corrections tracking, and the capability to save and reload incomplete forms. The DCC will also draft a comprehensive data management manual that includes detailed instructions and provide training and technical assistance. Participants will be identified by a study ID only. Site will be required to store hard-copy source documentation separately in a secured, locked cabinet.

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 can 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. Data will be backed up at regular intervals, with full transaction log files in use, and copies of the data will be stored offsite with a secure service. Servers will be migrated to a new host in the event of a hardware failure. All servers are behind an enterprise firewall and access must be granted through the firewall even within the University network.

Human Participants

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.

Capacity to provide informed consent will be assessed prior to randomization and will primarily be determined by Glasgow Coma Scale (GCS). Potential subjects with a GCS of less than 15 will be considered unable to consent. Potential subjects with a GCS of 15 will undergo a GOAT assessment, performed by a study investigator or neurosurgery CRC. A score of 74 or below will be considered unable to consent. For subjects that are determined to be unable to consent, assent will be obtained when applicable. The study team will also attempt to identify an appropriate LAR to provide prospective informed consent. If a LAR is identified within the 2-hour period after initial CT scan in the ED, this individual will be approached for proxy consent. If not, the patient will be enrolled under EFIC. If a potential subject has a GCS of 15 and scores 75 or above on the GOAT, we will presume s/he is capable of providing direct informed consent and will seek to obtain informed consent via a physician investigator.

Community consultation as determined by the IRB will be undertaken prior to final IRB approval. We will utilize the 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 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 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.

For additional details regarding the application of EFIC, procedures for notification and consent, and participant withdrawal, please refer to Appendix I – CriSP-TBI EFIC Plan.

Study Stopping Points:

The following describes the study stopping points regarding participant involvement:
1) if the study procedures appear to be medically harmful
2) if the participant no longer wishes to participate
3) if the study is cancelled

Institutional Review Board: An IRB will be utilized at the University of Pittsburgh for the regulatory needs of studies.

Training and Participating Site Coordination**:** As the clinical coordinating center for the trial, 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. Trial enrollment and maintenance of data integrity will be assessed monthly using the web-based data platform. Trial screening, enrollment and data completeness and accuracy will be accessed at 6 months by the CCC.

Safety Monitoring:

Adverse Event 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.

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. 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 participant 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 participants or significantly compromises the quality of the research data. Incidents of non-compliance on the part of the participant 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 participant's participation in research; and places participants or others at greater risk of harm (including physical, economic, or social) than was previously known or recognized.

Assessing and Reporting Adverse Events (AEs): Adverse events will be reviewed 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 study participation termination. If reportable adverse events occur, they will be recorded on the adverse event case report form in the electronic data capture system. 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 many 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 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), 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.

Quality Control, Assurance and Confidentiality

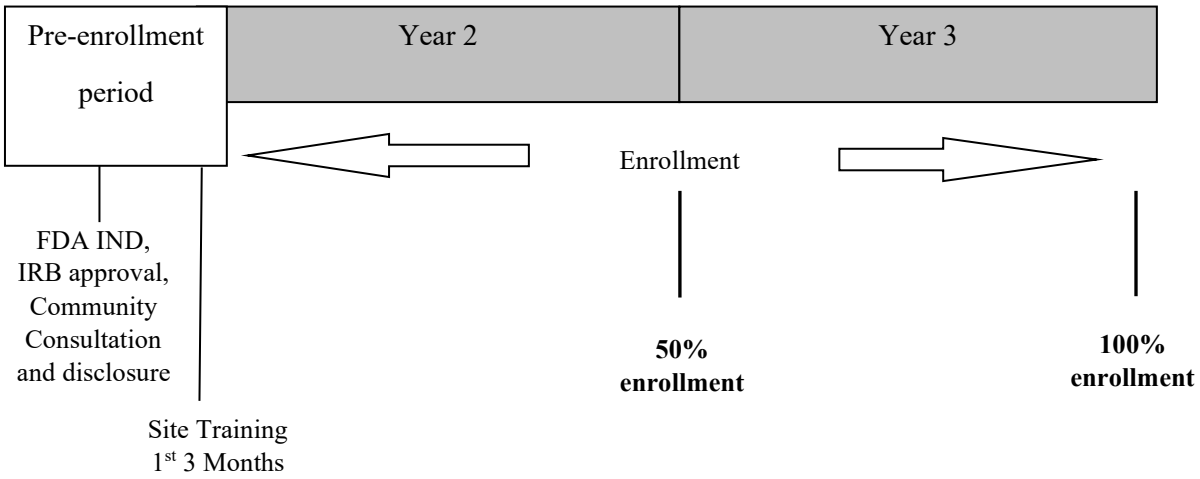
Protocol Compliance**:** The participating study site Investigators will not deviate from the protocol for any reason without prior written approval from the IRB except in the event of the safety of the research participant. In that event, the study site Investigator will notify the IND Sponsor and reviewing 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 participants 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 intervention, the relative focused inclusion criteria, and the short intervention period, we expect few protocol deviations as compared to other trials. If monitoring reports demonstrate evidence of continuing protocol deviations, we will analyze them and determine the best corrective action plan. 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 occur, retraining will be done. The problems will be discussed with Principal Investigator, the DOD and the FDA to see if the protocol needs amended or recruitment put on hold.

Privacy and Confidentiality: The study Principal investigator and members of the research team will make reasonable effort to ensure the research participants' confidentiality. Participant name and other identifiable information will be kept in a secure, locked, limited access area.

Investigator Responsibilities: The study Principal investigator 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.

Timetable:



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