Linking Investigations in Trauma and Emergency Services

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Executive Summary

The LITES Network is an operational trauma center consortium which has the expertise, track record and confirmed capabilities to conduct prospective, multicenter, injury care and outcomes research of relevance to the Department of Defense (DoD).

Hemorrhage and Traumatic Brain Injury (TBI) are responsible for the largest proportion of all trauma-related deaths. It is the poly-trauma patient who suffers both hemorrhagic shock and traumatic brain injury where a paucity of evidence exists to direct treatment, limiting the development of beneficial trauma practice guidelines.

The use of Whole Blood (WB) for early trauma resuscitation has been touted as the 'essential next step' in the evolution of trauma resuscitation. Despite its historical and more recent use, little is known regarding WB's benefit relative to the 'current practice' ratio-based blood component therapy in the acutely bleeding patient, and even less is known regarding its effects in patients with TBI.

AIM#1: Evaluate patient centered outcomes associated with early whole blood resuscitation practice as compared to component resuscitation in poly-trauma patients with hemorrhagic shock and further characterize outcome benefits in those with traumatic brain injury. Whole blood Clinical Practice Guidelines will be prepared, including staff training resources, and provided for use by the Government.

AIM#2: Characterize blood pressure and resuscitation endpoints during the acute resuscitation phase of care and the associated/attributable outcomes for traumatic brain injury in patients with hemorrhagic shock.

General Hypothesis #1: Whole blood resuscitation will be associated with improved mortality and resuscitation outcomes in poly-trauma patients and long term neurological outcome in those patients with traumatic brain injury as compared to those resuscitated with component therapy.

General Hypothesis #2: Differences in prehospital and acute phase resuscitation systolic blood pressure will be associated with differential outcomes in patients with traumatic brain injury at discharge and at 6 months.

Study Design: The LITES network will perform a multicenter, prospective, observational cohort study over a 4-year period to determine the impact of whole blood resuscitation in trauma patients with hemorrhagic shock at risk of large volume resuscitation with and without TBI. Early whole blood resuscitation will be compared to standard component resuscitation. The study will also further characterize blood pressure and resuscitation endpoints in poly-trauma

patients with traumatic brain injury. Trauma sites with appropriate characteristics will be selected within the LITES Network across the country.

Study Setting: The study will be performed utilizing busy level I trauma centers within the LITES Network located across the country, at sites where either whole blood has currently been incorporated into standard of care or where component blood transfusion is being utilized for patients in hemorrhagic shock at risk for large volume resuscitation.

Study Population: The study will focus on patients who suffer blunt or penetrating injury, transported to a Task Order 002 participating LITES trauma center with evidence of hemorrhagic shock at risk of large volume blood resuscitation.

Background

The LITES Network is an operational trauma center consortium which has the expertise, track record and confirmed capabilities to conduct prospective, multicenter, injury care and outcomes research of relevance to the Department of Defense (DoD). Clinical trials from the point of injury in the prehospital arena through the trauma bay and operating theatre, through ICU and beyond discharge are feasible and critical to the overall goals of the network. Novel capabilities include prehospital point of care testing for shock severity and sequential coagulopathy measurements. The network and leadership have a track record of Exception From Informed Consent (EFIC) trials for planned emergency research and expertise with those injury subtypes including traumatic brain injury, hemorrhagic shock and coagulopathy of trauma, poly-trauma and severe extremity trauma. In addition to the track record and proven capabilities, the LITES Network uses a central IRB and efficient methods to minimize time, resources, cost and regulatory burdens to improve recruitment, consent rates and ease of data acquisition in order to promote successful execution of those task orders provided to the network from the DoD.

Traumatic injury represents an incredible health care burden in the United States and worldwide.[1] Hemorrhage and Traumatic Brain Injury (TBI) are responsible for the largest proportion of all trauma-related deaths.[2-4] Despite advances in trauma resuscitation and brain injury management, few therapeutic interventions are available to reduce the downstream morbidity and mortality attributable to these injury patterns.[5-7] It is the poly-trauma patient who suffers both hemorrhagic shock and traumatic brain injury where a paucity of evidence exists to direct treatment, limiting the development of beneficial trauma practice guidelines.

Ongoing traumatic blood loss is complicated by trauma induced coagulopathy which results in further unbridled hemorrhage and resultant shock and organ dysfunction.[8-17] Secondary to increasing evidence and knowledge, in-hospital resuscitation of traumatic hemorrhage has

changed over the past decade to reduce the coagulopathic response to ischemia and tissue injury.[18-23] The underlying principle of current resuscitation practice focuses on preventing or reversing the effects of coagulopathy with the early use of a balanced component transfusion strategy (1:1:1 - plasma: packed red blood cells: platelets).[24] This reconstituted strategy has also been coined 'whole blood-like' resuscitation despite being inferior from a compositional standpoint relative to Whole Blood (WB).[25-26] The use of WB was historically the gold standard for treating hemorrhagic shock during World War I and II, prior to sweeping changes in blood banking practice.[27] The use of WB for early trauma resuscitation is making a resurgence, primarily based upon the military experience[28-32] and has been touted as the 'essential next step' in the evolution of trauma resuscitation.[26,33] Despite its historical and more recent use, little is known regarding WB's benefit relative to the 'current practice' ratio based blood component therapy in the acutely injured patients and even less is known regarding its effects in patients with TBI.

Permissive hypotension has been thought to improve outcome in injured patients with hemorrhagic shock in the prehospital and acute resuscitation phase of treatment allowing for the ability to obtain surgical control of bleeding while minimizing ongoing hemorrhage.[34-37] Despite this benefit for hemorrhagic shock patients, hypotension has been consistently shown to be associated with worse outcomes in patients with TBI.[38-40] Interestingly, newer animal data suggests permissive hypotension may be beneficial in a swine TBI model.[41] The majority of prior, high level TBI trials have excluded patients with concomitant hemorrhagic shock. Prospective evidence and long term TBI outcome data are lacking for these complex poly-trauma patients and the most appropriate blood pressure and most efficacious resuscitation target for patients with TBI and acute hemorrhage remain poorly characterized.

Preliminary Data

Based upon the belief that early whole blood resuscitation represents the most efficacious hemostatic resuscitation product for the management of hemorrhage, the University of Pittsburgh started initially with 2 units and demonstrated feasibility and safety of a WB early resuscitation program[30,42] and now has 4 units of cold stored, low titer, platelet replete-leukocyte reduced, group O-WB for urgent release in the emergency department, without the need for blood typing or cross matching, for patients in hemorrhagic shock. We have currently transfused over 169 patients with over 296 units of WB without evidence of safety concerns. We plan to increase our urgent release availability to 6 units of WB within the next 6 months. We have simultaneously been monitoring

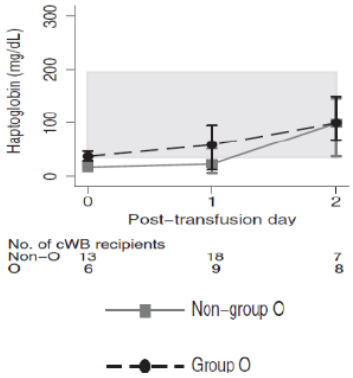


Figure 1

WB patients for hemolytic side effects from ABO mismatched whole blood.[42] In 27 non-group O patients, there were no significant differences in laboratory hemolysis markers. (**Figure 1**) These preliminary and published data verify the feasibility and safety of this type of intervention in patients with hemorrhagic shock, providing the backdrop for the successful execution of the proposed observational cohort. Other trauma centers in the LITES Network are initiating and executing similar WB programs which we will utilize for the current proposal.

Objectives/Specific Aims/Hypothesis

Due to the need to robustly characterize the safety and efficacy of cold-stored, urgent release, whole blood resuscitation in poly-trauma patients and provide essential insight into the most appropriate resuscitative target for injured patients with both hemorrhagic shock and TBI, we propose the following primary AIMs.

AIM#1: Evaluate patient centered outcomes associated with early whole blood resuscitation practice as compared to component resuscitation in poly-trauma patients with hemorrhagic shock and further characterize outcome benefits in those with traumatic brain injury.

AIM#2: Characterize blood pressure and resuscitation endpoints during the acute resuscitation phase of care and the associated/attributable outcomes for traumatic brain injury in patients with hemorrhagic shock.

Hypothesis #1A: *Whole blood resuscitation will be associated with a lower 4 hour mortality in poly-trauma patients as compared to those resuscitated with component therapy.*

Hypothesis #1B: *Whole blood resuscitation will be associated with a lower incidence of 12 hour and 24 hour mortality, a lower incidence of death from exsanguination, incidence of MOF, nosocomial infection, improved transfusion ratios, lower overall blood transfusion requirements and shorter time to hemostasis as compared to those resuscitated with component therapy.*

Hypothesis #1C: *Whole blood resuscitation will be associated with an improved Glasgow Outcome Score-Extended at 6 months post injury as compared to those resuscitated with component therapy in patients with traumatic brain injury.*

Hypothesis #2A: *A nadir prehospital and acute phase resuscitation systolic blood pressure greater than or equal to 120 mmHg will be associated with improved traumatic brain injury outcomes at discharge and at 6 months.*

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Hypothesis #2B: *The magnitude of the dose depth curve of systolic blood pressure during the prehospital and acute phase resuscitation will be associated with neurological outcome differences at discharge and at 6 months following traumatic brain injury.*

Research Design and Methods

Study Design: The LITES Network will perform a multicenter, prospective, observational cohort study over a 4 year period to determine the impact of whole blood resuscitation in trauma patients with hemorrhagic shock at risk of large volume resuscitation with and without TBI. Early whole blood resuscitation will be compared to standard component resuscitation. The study will also further characterize blood pressure and resuscitation endpoints in poly-trauma patients with traumatic brain injury. Six trauma sites with appropriate characteristics will be selected from network sites across the country. (**Figure 2**)

Figure 2

Study Setting: The study will be performed utilizing busy level I trauma centers from within the LITES Network located across the country, at sites where either whole blood has currently been incorporated into standard of care or where component blood transfusion is being utilized for patients in hemorrhagic shock at risk for large volume resuscitation. Due to the paucity of trauma centers who are currently utilizing whole blood for trauma patients as standard of care, the potential to incorporate additonal sites may be required over time.

Study Population: The study will focus on patients who suffer blunt or penetrating injury, transported to a Task Order 002 participating LITES trauma center with evidence of hemorrhagic shock at risk of large volume resuscitation.

Inclusion Criteria: Patients with blunt or penetrating injury who meet the following criteria: 1, 2, and 3

1) Has 2 or more of any of the following:
    a. Hypotension (systolic blood pressure ≤ 90 mmHg) in the prehospital setting or within 60 minutes of hospital arrival,
    b. Penetrating mechanism,
    c. FAST abdominal 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 setting or within 60 minutes of hospital arrival.

AND

2) Taken to the Operating Room (laparotomy, thoracotomy or vascular exploration) or Interventional Radiology within 60 minutes of arrival.

AND

3) Blood/blood component transfusion in prehospital setting, ED or OR within 60 minutes of arrival.

Exclusion Criteria:

1) Age < 15
2) CPR > 5 consecutive minutes without ROSC
3) Penetrating brain injury with brain matter exposed
4) ED death
5) Known pregnancy
6) Known Prisoners

Inclusion and exclusion criteria will be assessed based on available information at the time of enrollment. Although all reasonable efforts will be made by the prehospital crew to either directly witness or obtain documentation of qualifying vitals, due to the nature of the emergency pre-hospital setting, there may be occasions where the prehospital medical crew must rely on verbal report of inclusion criteria, including qualifying vitals, from the referring hospital or EMS agency. In these instances, if, after subsequent review of outside hospital and/or EMS agency documentation, it is determined that the subject did not meet inclusion criteria and/or met exclusion criteria, the subject will remain enrolled in the study based on the information available at the time the subject was enrolled in the study.

Recruitment and Consent

Initial blood sampling must be performed as early as possible after arrival (0 (+ up to 2), 4 (+/- 2) and 24 hours (+/- 12)). Because the initial early samples will be drawn before many subjects are able to consent due to their illness, and before surrogate decision-makers are typically available to consent, we are requesting waivers of consent to be used for: A) initial medical record review to verify eligibility, and B) 3 blood samples will be taken within 36 hours of arrival. A Waiver of HIPAA Authorization is also requested for the extraction of research data from the medical record during the first 36 hrs of admission. Subjects whose medical conditions improve to the point of being able to make their own medical decisions will sign a consent to continue further study-related procedures. Subjects who remain critically ill, receiving continuous or intermittent sedatives, who are obtunded/disoriented from illness or injury, or are unable to dictate their own care will have proxy consent obtained from their previously appointed power of attorney (if one

exists) or the subject's legally authorized representative. If there is no designated LAR, a proxy will be selected consistent with state laws.

Waiver of Consent [A] Medical record review for the identification of potential subjects

The research involves no more than minimal risk to the subjects **[45 CFR 46.116 (d)(1)].**

The screening procedure poses minimal risk to the subjects. It involves a chart review to determine eligibility that will be performed on the medical records or by the attending/treating clinician(s).

The only risk is breach of confidentiality that will be minimized by removing all patient identifiers and replacing them with a research code number; and storing the coded, de identified data on a secure pass word protected data base behind a University firewall.

The waiver or alteration will not adversely affect the rights and welfare of the subjects **[45 CFR 46.116 (d)(2)].**

Access to and use of patient medical record information will be limited to the research study investigators and their staff who already have access to this PHI based on the clinical responsibilities of the principal investigator that extends to their research teams.

The research could not practicably be carried out without the waiver or alteration **[45 CFR 46.116 (d)(3)].**

It is not practicable to try to obtain consent simply to identify eligible patient participants

Whenever appropriate, the subjects will be provided with additional pertinent information after participation **[45 CFR 46.116 (d)(4)].**

It is unlikely that any information pertinent to the trauma patient's care will be obtained through this limited recruitment activity.

Waiver of Consent [B] Blood sampling during the first 36 hrs of admission.

The research involves no more than minimal risk to the subjects **[45 CFR 46.116 (d)(1)].**

Blood samples for this study will be obtained in conjunction with draws for clinical care whenever possible. In cases where it is not possible to coordinate research sample collection with clinical sample collection, trauma patients will already have an existing central line that can be utilized to

obtain the sample or venipuncture will be performed by clinically trained personnel using aseptic techniques.

Obtaining three 20 ml samples of blood will pose only minimal risk to these patients as collection of the samples will be via existing vascular access using aseptic techniques. The risk of a breach of confidentiality will be minimized by removing all patient identifiers and replacing them with a research code number; and storing the coded, de-identified data on a secure pass word protected data base behind a University firewall.

The waiver or alteration will not adversely affect the rights and welfare of the subjects **[45 CFR 46.116 (d)(2)].**

The acquisition of blood samples will be performed by trained and experienced research staff, under the oversight of the Principal Investigator, a physician with a research focus on coagulopathy, massive transfusion and clinical outcomes of traumatic injury

The research could not practicably be carried out without the waiver or alteration **[45 CFR 46.116 (d)(3)].**

Understanding the early response to whole blood administration, component therapy and hemorrhagic shock is an important focus of this proposal since early factors influence later events such as the development of multiple organ failure. Identifying and discovering which early mechanistic biomarkers might influence outcomes in this population is an important part of this study.

Samples are required in the first 36 hours in order to determine the underlying mechanisms of whole blood benefit, which is one of the main objectives of the study. Sampling needs to occur approximately at the time of whole blood transfusion and soon after. Whole blood and component arm transfusion, in these severely injured trauma patients, will for the majority of patients occur within the first 4 hours of admission. Sampling at the proposed time points in the first 36 hours are essential and have to occur in relationship to this early whole blood and component transfusion window. Sampling beyond these early time points will not allow the main objectives of the study to be accomplished.

Whenever appropriate, the subjects will be provided with additional pertinent information after participation. **[45 CFR 46.116 (d)(4)].**

Subjects whose medical conditions improve to the point of being able to make their own medical decisions will sign a HIPAA-compliant consent to continue further study-related procedures. Subjects who remain critically ill, receiving continuous or intermittent sedatives, who are

obtunded/disoriented from illness or injury, or are unable to dictate their own care will have proxy consent obtained in compliance with local regulations.

A Waiver of HIPAA Authorization is also requested and justified, to be used in conjunction with the Waiver of Consent [B], for the extraction of research data from the medical record.

***To ensure that this research use of the PHI involves no greater than minimal risk to privacy, describe your plan to protect patient-subject identifiers from improper use or disclosure*. [45 CFR 164.512 (i)(2)(ii)(A)(1)]**

All electronic data will be stored on a secure password protected server. Each subject will be given a unique study identifier, which will be used for all patient samples and all clinical data sheets. The key to identify subjects with their unique study number will be kept on a secure drive and only accessed by the PI, co-investigators or their designees according to the University of Pittsburgh and UPMC policies.

***Describe your plan to destroy patient-subject identifiers at the earliest opportunity consistent with the research. Indicate at what point in the research those identifiers will be destroyed. If applicable, provide a health, research or legal justification for retaining the identifiers*. [45 CFR 164.512 (i)(2)(ii)(A)(2)]**

At the time of data entry, all patient identifiers will be stripped and the data will be entered in a computerized database by code study number and all other records will be destroyed. Any info collected in hard copies will be secured in a locked area until data entry is completed. Only the PI, co-investigators or their designees will have access to this password protected database. A linkage to the actual patient will be kept on a separate secure password protected server.***Provide your assurance that this information will not be reused or disclosed to any other person or entity (i.e., other than the listed investigators and their research staff), except as required by law, for authorized oversight of the research study, or for other research for which the IRB has granted a waiver of the written HIPAA authorization.* [45 CFR 164.512 (i)(2)(ii)(A)(3)]**

All information generated in the course of the study will be accessed by the investigators or their designees according to the local site policies. Any sharing outside the University will be done with deidentified data.

***Why could this research not practicably be conducted unless the waiver of written HIPAA authorization is granted?* [45 CFR 164.512 (i)(2)(ii)(B)].**

Understanding the early response to whole blood administration, component therapy and hemorrhagic shock is an important focus of this proposal since early factors influence later events such as the development of multiple organ failure. Thus it will be necessary to establish baseline parameters during this time point, in order to assess the effect of whole blood versus component blood products on outcomes such as time to hemostasis, nosocomial infection or transfusion reaction. Extraction of research data during this early period will be essential to understand these processes.

Why could this research not practicably be conducted without access to and use of the identifiable medical record information? **[45 CFR 164.512 (i)(2)(ii)(C)].**

It is not possible to conduct this time-sensitive research in the Emergency Department and ICUs unless we are able to collect real time data to meet the outcomes associated with whole blood vs blood component therapy such as time to hemostasis, nosocomial infection, transfusion reaction and multiple organ failure.

Explain why the nature and amount of the medical record information that will be collected is felt to be the minimum necessary in order to conduct this research study. **[45 CFR 164.514 (d)].**

Only medical information that is pertinent to the outcomes will be collected.

If no appropriate legally authorized representative can be identified, the subject's ability to provide direct consent will be assessed until the time of hospital discharge. For subjects with some decision-making ability but who still require proxy consent, subjects' assent for participation may be obtained verbally. If the subject improves to the point of being capable of his or her own medical decision-making, the subject's consent will be obtained to continue participation. A copy of the informed consent document may be placed in the medical record. The original informed consent document will be kept with the study records in a locked file cabinet and a copy given to the subject or the subject's legally authorized representative. Consent and proxy consent will be obtained by the investigators listed on the first page of the consent document or properly trained research staff.

In cases where the LAR is not present in the hospital, the consent will be obtained by phone/fax or electronically. The study will be discussed with the LAR over the telephone. If the LAR agrees, the consent form (ICF) will be e-mailed or faxed or texted to the number provided by the LAR. The research staff will go over the ICF with the Legally Authorized Representative. If the LAR agrees to participate in the research, the LAR will sign the ICF and send back to the research staff by fax, text or scanned by e-mail. In cases where the proxy does not have access to a scanner or fax, they may take an electronic picture of the signed signature page and forward the

same to research personnel. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the informed consent will be sent via trackable means. The letter will be sent via trackable means and documentation of the addressee and date of mailing and the delivery confirmation with will be kept in the study folder. The subject or their LAR will return the consent using a study provided postage paid envelope. If a signed consent document is not obtained, ~~we don't receive any signed~~ no research activities will be performed nor data will be extracted from the medical record, beyond 36 hours period covered by the Waivers of Consent and HIPAA. Samples and data acquired under those Waivers will be retained.

Whole Blood Transfusion Sites: Busy, Level 1 trauma centers from within the LITES Network will be selected based upon the ability to enroll patients with the proposed inclusion and exclusion criteria who have already implemented or are in the direct process of implementing an urgent release whole blood resuscitation protocol and are able to perform all necessary requirements for the planned prospective cohort study proposed. Those sites with the capabilities to deliver at least 4 units of WB will be selected for participation with preference given to ≥ 6 units urgent release WB capabilities. WB sites will be selected based upon the ability to enroll 33% of patients for the overall cohort study. As WB resuscitation becomes increasingly more widely adopted, there exists the potential to include additional WB sites from within the network as respective institutional practice changes over the 4 year time point of the study. Similarly, there exists the potential to incorporate additional trauma sites into the LITES network based upon their abilities to enroll poly-trauma patients in hemorrhagic shock and the utilization of WB resuscitation. As different trauma sites may utilize differing WB products with different titer levels, matching processes, and leukocyte reducing capabilities, these WB characteristics will be documented for all sites and for all WB units and respective patients enrolled.

Component Transfusion Sites: Busy, Level 1 trauma centers from within the LITES Network will be selected based upon the ability to enroll patients with the proposed inclusion and exclusion criteria who currently utilize initial ratio based resuscitation (1:1:1 or 1:1:2) for patients at risk of large volume transfusion and are able to perform all necessary requirements for the planned prospective cohort study proposed. There is the potential for sites to differ based upon their current massive transfusion protocol and these standard practices will be documented for each site.

Primary TBI Subgroup Stratification: Presence or absence of Traumatic Brain Injury (TBI) will be the principle subgroup stratification for the study. Presence of TBI will be based upon CT imaging results (classification: subarachnoid, subdural, intracerebral hemorrhage, intracranial injury, epidural, +/- shift, multifocal with specific classification) and TBI severity will be characterized and grouped by GCS, Abbreviated Injury Severity (AIS) coding, ICD-10 head region severity scores

and Rotterdam CT scores. The data coordinating center will collect de-identified serial head CT images (first two performed) from all participating sites in patients with a head abbreviated injury score of 2 or greater (head AIS >2). These images will allow the determination of Rotterdam CT head scores to appropriately classify traumatic brain injury severity. Serial head CTs (first two) will also be assessed for progression of injury. An independent and blinded neuroradiologist from the University of Pittsburgh will provide the classification of brain injury.

Due to the nature of the population being studied, there will be patients who have clinically evident TBI but who do not have a head CT completed due to clinical intervention being a higher priority than diagnostic imaging. Often when patients require urgent clinical interventions, diagnostic scans (including CTs) are deferred until the patient is stabilized and the emergent issue is resolved. Unfortunately, this means that sometimes a patient expires during intervention, and a CT is never obtained. Therefore, patients who present in extremis with a clinically obvious TBI (eg: unhelmeted motorcyclist, falls from height, etc.) will be included in the TBI sub-group even if they do not have head CTs completed.

Primary Study Outcome: The cohort study will be principally powered using 4 hour mortality as the primary outcome. This outcome was found to be significantly different across treatment arms in the recent PROPPR trial and early mortality time points have recently been recommended and deemed most appropriate for hemorrhagic shock clinical trials.[24,43] Promoting survival beyond this time period may represent the critical period that is required for an injured patient to be transported to a higher echelon of care, particularly when injury occurs in austere environments.

Secondary Non-TBI Clinical Outcomes: Secondary clinical outcomes will include 12 hr mortality, 24hr mortality, 28 day mortality, time to hemostasis (defined by a WB or PRBC transfusion rate; ≤ 1unit/hour and surgeon directed intraoperative assessment), death from exsanguination/hemorrhage, blood and blood component transfusion requirements (over 1st four hours and total at 24hrs), Multiple Organ Failure, nosocomial infection, transfusion reaction, venous thromboembolism (VTE), ICU free days and ventilator free days.

TBI Specific Outcomes: For the overall TBI subgroup, the principle outcome will be 6 month Extended Glasgow Outcome Scale (GOS-E). Additional TBI specific outcomes will include hemodynamic parameters (serial systolic and diastolic blood pressure and heart rate measurements), prehospital, arrival, serial and discharge Glasgow Coma Scale scores, need for craniectomy/craniotomy, need for mannitol administration, need for paralysis, need for barbiturate coma, need for hypertonic saline administration, need for ICP monitoring, ICP pressures (initial, max daily x 7 days), TBI progression based upon serial CT imaging in initial 48 hours and Galveston Orientation and Amnesia Test (GOAT score) at discharge. Each accrual site will transfer the TBI patient's name, contact information, and basic injury characteristics, GOAT results, and discharge disposition to the Clinical Coordinating Center in Pittsburgh.

Suicidal or emotionally distressed participants: If a participant reports suicidal ideation during the GOS-E, a risk assessment will be performed immediately by a trained neuropsychological technician under the supervision of a licensed neuropsychologist. If the participant is found to NOT be at imminent risk, resources will be given to the participant in the form of the Suicide Hotline and The Brain Injury Association of America website URL. The technician will compose a 'Note To File' detailing their assessment and will make the other study team members aware of their assessment. If the participant is found to be at imminent risk, the technician will encourage the participant to go to their nearest local emergency room. These actions will be noted in the case file.

Predefined Subgroups: Predefined subset analyses in addition to principle TBI subgroup analysis will be performed looking at 1) patients enrolled from the scene of injury versus those enrolled from a referral hospital, 2) patients with a preinjury history of vitamin K antagonist medication versus those without, 3) patients with preinjury history of antiplatelet medication versus those without, 4) patients with preinjury history of novel anticoagulant use versus those without, 5) patients who ultimately did or did not require massive transfusion (≥ 10 units blood in first 24hrs), 6) patients who ultimately did or did not meet a critical transfusion threshold of ≥ 4 units PRBCs or whole blood in a 2 hour time period, 7) patients who ultimately did or did not require ≥ 6 units blood in first 24hrs, 8) patients who did or did not receive leukocyte reduction WB products, 9) TBI patients who did or did not receive a craniectomy/ craniotomy, 10) TBI patients who did or did not require ICP monitoring. 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.

Specific Outcome Definitions:

Denver MOF Score: The appropriate classification and timing of mortality will be captured in the data elements collected as described above. Of similar importance is the morbidity which ensues for those who survive their initial injury. Data elements that include the ability to calculate the Denver post-injury multiple organ failure score[44-47] will be collected over the first 7 days for those who are admitted to the ICU > 48 hours. (**Figure 3**) A total score > 3 will be considered MOF and the daily score will be determined up until post-injury day 7 or ICU discharge. Patients not residing in the ICU will be given a score of 0. If data elements are missing on specific days, the individual score for that missing component will be obtained from the prior day's laboratory values.

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary PaO2/FiO2 ratio	> 300	300 - 201	200 - 101	< 101
Renal Creatinine (umol/L)	<159	160 - 210	211 - 420	> 420
Hepatic Total Bilirubin (umol/L)	< 34	34 – 68	69 - 137	> 137
Cardiac Inotropes	No inotropes	Only one inotrope (small dose)	Any inotrope at moderate dose	Any inotrope at large dose

Figure 3.

Nosocomial Infection/Sepsis Data Elements: Nosocomial infections and sepsis outcomes will be derived from microbiology records and based upon positive culture evidence including bronchoalveolar specimens, blood cultures, wound cultures, organ space cultures and urinary tract cultures. Over the first 30 days of admission, quantification and location of specimen and classification of organism (Gram+, Gram-, species) will be collected. Quantitative thresholds for ventilator associated pneumonia, catheter related blood stream infections and urinary tract infection will be utilized as determined by the most recent CDC criteria and guidelines (www.cdc.gov/nhsn).

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 WB or PRBCs in a 60 minutes time period in the first 4 hours following arrival. Surgeon directed time to hemostasis will 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.

Death from Exsanguination/Hemorrhage: Those patients who succumb on the operating table, IR suite or ICU due to uncontrolled coagulopathy or hemorrhage in the first 4 hours from arrival will have their mortality classified as exsanguination/hemorrhage. This will be determined by the individual trauma surgeon at the time of the event.

Acute Hemolytic Transfusion Reaction: We will utilize and characterize acute hemolytic transfusion reactions as defined by the CDC/National Healthcare Safety Network (NHSN) Hemovigilance Surveillance definition (www.cdc.gov/nhsn).

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Galveston Orientation and Amnesia Test (GOAT): For TBI subjects, we will obtain the GOAT score at the time of discharge and the calculated score per standard methods.[48] (**Figure 4**) 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 subject is able to provide continuing participation consent if consented by proxy.

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

Figure 4

Extended Glasgow Outcome Scale (6 months-GOSE): For TBI subjects, the GOSE score will be obtained at 6 months +/- 1month by hone survey or direct patient contact, whichever is feasible. For those TBI subjects 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 is able to characterize 6 month functional status into 8 well defined categories as shown in (**Figure 5**).

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 +

Figure 5

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.*

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Clinical Laboratory Endpoints: Measurements of hemostasis (TEG, PT/PTT, INR; 0 hour(+ up to 2 hours), 4 hour (+/-2 hours) and 24 hour (+/-12 hours)) for all patients and hemolysis labs (LDH, haptoglobin, bilirubin; 0 hour (+up to 2 hours), 4 hour (+/- 2 hours), and 24 hour (+/- 12hours)) for all patients will be obtained. Plasma samples for mechanistic outcomes will be drawn, stored, aliquoted and banked. The timing of all laboratory draws will follow local state and central IRB guidelines and local IRB guidelines at those sites who do not cede those guidelines to the central IRB at the University of Pittsburgh. The specific planned timing of draws are shown in (**TABLE 1**).

Screening/Outcome Data and Sample Collection: Patients will be screened for inclusion and exclusion criteria for the cohort study at the time of or soon after trauma center arrival and will undergo early blood sampling (Arrival + up to 2hrs). LITES Network sites selected for the prospective cohort study will have the capabilities to follow the patient to the OR, IR suite or ICU to obtain samples/labs and to record and monitor ongoing resuscitation, blood and blood component transfusion, mortality time points, time to hemostasis and death due to exsanguination for up to 4 hours from arrival or until hemostasis is obtained or patient death occurs. Due to the early requirement of initial blood samples for this cohort study, a waiver of consent for the initial patient screening and early blood draws (first 36hrs post-injury) will be obtained from the central IRB. When available, blood samples will be drawn from an indwelling catheter (arterial or venous). If no indwelling catheter is available, then venipuncture will be performed following standard state and IRB requirements. Clinical laboratory samples will be sent at each LITES Network site following each sites laboratory guideline/requirements. Blood samples for storage will be drawn, centrifuged, separated, processed, and stored at -80°C for batched shipping. The schedule of proposed data and sampling can be found in (**TABLE 1**).

+TBI Subjects

TABLE 1.

Procedures/Measurements	Prehospital	Arrival (+up to2 hours)	4 hours (+/-2 hours post admission	24 hours (+/-12 hours) post admission	At discharge	At 6 months (+/- 1 monht)
Whole blood administration		x	X			
Component therapy administration		x	X			
Resuscitation data (WB, component transfusion)	x	x	X	x	x	
Survival		x	X	x	x	x
Mechanistic Banked Samples		x	X	x		
Hemostasis (PT, INR, TEG)		x	X	x		
Hemolysis Labs (Lactate Dehydrogenase, haptoglobin, bilirubin)		x	X	x		
Mechanistic Biomarkers		x	X	x		
CBC		x	x	x		
Serial Vitals (GCS, Blood pressure, Heart rate)	x	x	X	x		
GOAT (Galvenston Orientation Amnesia Test) +					x	
Extended Glasgow Coma Scale+						x

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Clinical Coordinating Center: Clinical Coordination specific for Task Order 002 will be performed by MACRO (Multidisciplinary Acute Care Research Organization) and its dedicated research team at the University of Pittsburgh, including all regulatory requirements, provider and coordinator training and monitoring.

Institutional Review Board: A central IRB will be utilized at the University of Pittsburgh for the regulatory needs of the prospective observational cohort. All current LITES Network sites have IRBs which have experience and engagement with central IRB procedures. A waiver of initial consent up to 36 hours for screening and early sampling will be obtained from the central IRB allowing early sampling prior to consent.

Data Coordinating Center (DCC): Data Coordination specific for Task Order 002 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.

Data Collection: Based upon the ability to appropriately execute AIMs I and II, the associated hypotheses generated and the primary and secondary outcomes proposed, the following data will be obtained on enrolled patients:

Demographic and Injury Data: Age, gender, race/ethnicity, socioeconomic status, mechanism of injury, ISS, AIS scores, serial vitals (blood pressure, heart rate, respiratory rate), presence of TBI, ICU days, ventilator day, length of hospital stay, patient medication and past medical history.

Prehospital Data: Time of injury, scene time, serial vital signs (GCS, blood pressure, heart rate, respiratory rate), transport characteristics, times and description of prehospital interventions (intubation, lines), medications, medic qualifications, crystalloid fluids, blood or blood component transfusion, adjuncts including tranexamic acid.

ED Data: Arrival time, serial vitals (GCS, blood pressure, heart rate, respiratory rate), procedures, meds, resuscitation requirements (crystalloid, blood or blood component), adjuncts including tranexamic acid, factor VII, PCC, fibrinogen, ED disposition.

OR Data: Procedures, operations, resuscitation requirements (crystalloid, blood or blood component), type of anesthesia, vasopressor requirement, adjuncts including tranexamic acid, factor VII, PCC, fibrinogen, disposition, serial vitals (blood pressure, heart rate), OR disposition, core temperature.

Resuscitation Data: Whole blood resuscitation, time of transfusion, WB characteristics (titer, blood type, matched/unmatched, leukocyte reduced, platelet sparing), component blood resuscitation, time of transfusion, transfusion ratios, adjuncts including tranexamic acid, factor VII, PCC, fibrinogen.

Outcome Data: 4 hour, 6 hour and 24 hour mortality, MOF score (7days), nosocomial infection, acute hemolytic transfusion reaction, cause of mortality, time to hemostasis, venous thromboembolism (VTE).

TBI Data: Serial GCS, TBI severity (AIS codes), TBI classification (subarachnoid, subdural, intracerebral hemorrhage, epidural, +/- shift, multifocal with specific classification) TBI progression, ICP data, operative intervention, paralysis, benzodiazepine coma, hypertonic resuscitation, GOAT and GOSE at discharge and 6 months respectively.

Eligible patients for the prospective cohort study will have de-identified data configured for compilation into the web based data entry platform with appropriate and all security measures in conjunction the DCC.

Mechanistic Banked Samples: Samples within the 0 hour (+ up to 2 hours), at 4 hours (+/- 2 hours) and 24 hours (+/- 12 hours) will collected and stored for analyses. We will perform batched sample analyses of enrolled patient subgroups +/- coagulopathy and +/- TBI across the receipt of WB vs. component therapy. We will measure markers of endothelial cell injury including Syndecan-1 and Hyaluronan, markers of neurological injury and neuron cell death including S100B protein and Neuron Specific Enolase (NSE), and end points of coagulopathy including Thrombin-antithrombin complex (TAT), activated Protein C (aPC), tissue Plasminogen Activator (tPA) and Plasminogen Activator Inhibitor (PAI-1).

Sample Tracking, Management and Storage: After sample obtainment, processing and storage, samples will initially be batched sent to the University of Pittsburgh biological sample repository where it will be tracked, managed and stored until the necessary translational or mechanistic measurement are performed. The CCC and DCC have a long track record of coordinating such processes.

Power Analysis: The prospective cohort study will utilize time to 4 hour mortality for its primary outcome to power the study. Based upon the 6 LITES Network sites admission history that will be utilized and their respective volume of hemorrhagic shock patients meeting inclusion and exclusion criteria and a 3.5 year enrollment time period, we plan to initiate sampling on 1,050 patients over the enrollment time period of the study. With an 85% consent rate which is an estimate based upon prior studies of similar nature, we will consent for participation 892 patients for the study. With an estimate baseline rate of 4 hour mortality of 11.1 % derived from the PROPPR study, there will be 90% power to detect a hazard ratio of 1.9.

Calculations are based on the primary aim of the study based on the following assumptions:

- Type I error rate of 0.05
- Two-sided alternative hypothesis

- 6 sites will be involved, three whole blood and three component sites
- Each site will enroll 175 participants in 3.5 years of enrollment, of which, 85% will be eligible for the study (149)
- The calculations are based on Cox proportional hazard model
- A 4 hour event rate in the control (non-whole blood) group of 0.111

The power calculations for these secondary aims are presented below. When reporting the results of the analyses, caution will need to be taken with respect to the interpretation of the findings since they are secondary in nature.

The secondary outcomes in Aim 1B include binary outcome, continuous outcomes, and time to event outcomes. For the binary outcomes, the odds ratio that can be detected is presented in Table 1. For the continuous outcome, the effect size that can be detected is 0.13. Finally, for the time to event outcomes, the hazard ratio that can be detected over a range of event rates in the control group is also presented in Table 1.

Table 1: Detectable Effect Sizes Event Rate in the Control Group

Event Rate	.1	.2	.3	.4	.5	.6
Odds Ratio	1.76	1.56	1.49	1.46	1.46	1.48
Hazard Rate	2.69	1.70	.37	.30	.27	.30

- For Aim 1C, a nonparametric analysis of variance will be used to compare the distribution of the GOS-E between the two groups. An effect size of 0.17 could be detected.
- For aim 2A, a nonparametric analysis of variance will be used to compare the distribution of the GOS-E between the two groups. An effect size of 0.28 could be detected.
- For aim 2B, a nonparametric correlation coefficient will be used to assess the association between GOS-E and the area under the systolic blood pressure curve. For each, a 95% confidence interval with a width of 0.19 can be estimated.
- For all secondary analyses, the type I error rate was set to 0.05, with a two-sided alternative hypothesis, and 90% power. For the Aim 1, the sample size will be 1,190. For Aim 2, the sample size will be limited to those with a traumatic brain injury. For the purposes of this study, this is expected to be 35% or a total of 417 participants.

Analyses

AIM#1: The analysis will begin by describing the baseline demographic and clinical characteristics of the overall population and then stratified by whole blood usage. The characteristics will be

compared among those who receive and who do not receive whole blood. 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) among those who receive and do not receive whole blood.

Hypothesis#1A: For the primary outcome, the time to death will be generated for each participant. 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 hierarchical Cox-proportional hazards regression model will be used to control for the within-institution clustering. The hierarchical Cox-proportional hazards regression model will then be used to assess the independent impact of whole blood on time to death after controlling for the clustering effect and potential confounding effects of baseline characteristics. The model will include main effects for whole blood usage and a propensity score for receiving whole blood. The propensity score for the use of whole blood will be generated using a boosted logistic regression model. The dependent variable in the model will be the use of whole blood and the independent variables will be the baseline characteristics of the population. The Cox-proportional hazards model will be used to estimate the cumulative probability of death 4 hours.

Hypothesis#1B: The analytic approach for the secondary outcomes included in Hypothesis#1B will vary based on the type of outcome. For binary outcomes (e.g., 12 hour and 24 hour mortality, death from exsanguination, incidence of MOF, nosocomial infection), the same analytic approach that was carried out for Hypothesis 1a will be implemented.

For continuous outcomes (e.g., transfusion ratios, blood transfusion requirements) a two-sided t-test for correlated means will be used to compare the means between those receiving and not receiving whole blood. A hierarchical analysis of variance model will be used to control for the within-institution clustering. The model will be used to assess the independent impact of whole blood after controlling for the clustering effect and the potential confounding. The model will include main effects for whole blood usage and propensity for receiving whole blood.

Finally, for time to event analyses (e.g., time to hemostasis), a bivariate hierarchical Cox proportional hazards regression model will be generated to compare the time to event between those receiving and those not receiving whole blood. Again, the hierarchical model will be used to control for within-institution clustering. In a second step, to determine the independent effect of whole blood after controlling for potential confounding effects, the propensity score will be added to the model.

Hypothesis#1C: A two-sided z-test for correlated proportions will be used to compare the distribution of GOS-E proportions between those receiving and not receiving whole blood. This

test will be used to control for the within-institution clustering. A hierarchical polytomous logistics regression model will then be used to assess the independent impact of whole blood after controlling for the clustering effect and the potential confounding effects of baseline characteristics. The model will include main effects for whole blood usage and propensity for receiving whole blood.

AIM#2: The analyses for the second aim will be restricted to the subset of participants who will be characterized as having a traumatic brain injury.

Hypothesis#2A: The analysis will begin by comparing the baseline characteristics of those with a prehospital and acute phase resuscitation systolic blood pressure greater than or equal to 120 mmHg to those who do not. For discrete variables, proportions will be generated and a chi-squared 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-test (Wilcoxon) test will be used to compare the means (distributions) among those who receive and do not receive whole blood.

A two-sided z-test for correlated proportions will be used to compare the distribution proportions of GOS-E at 6-months between those with a prehospital and acute phase resuscitation systolic blood pressure greater than or equal to 120 mmHg to those who do not. A hierarchical polytomous logistics regression model will be used to control for the within-institution clustering. The model will be used to assess the independent impact of whole blood after controlling for the clustering effect and the potential confounding effects of baseline characteristics. As was done in Aim#1A, the propensity for a prehospital and acute phase resuscitation systolic blood pressure greater than or equal to 120 mmHg will be generated using a boosted logistic regression model which will include all baseline characteristics, including site and whole blood usage. The same analytic approach will be used to measure outcomes at discharge except a hierarchical logistic regression model will be used.

Hypothesis#2B: The area under the curve of systolic blood pressure during the prehospital and acute phase resuscitation will be generated for each study participant. The analysis will begin by comparing the baseline characteristics with the area under the curve. For discrete variables, bivariate linear regression models will be generated (area under the curve as the dependent variable and the discrete baseline characteristic as the independent variable). For continuous characteristics, the correlation will be assessed.

Hierarchical models will be used to adjust for within-institution clustering. Hierarchical bivariate linear regression models will be used to assess the association of baseline characteristics associated with area under the curve. A stratified propensity analysis will be used to estimate the association of area under the curve with GOS-E at six months. A hierarchical linear regression

model will be generated using the area under the curve as the dependent variable and the baseline characteristics as independent variables to generate an estimated area under the curve (propensity score) for each subject. The population will then be separated into five strata of equal sample size, based on the propensity. Within each stratum, the association of the area under the curve with outcome will be assessed using a hierarchical polytomous logistic regression model (outcome: GOS-E at six months, independent variable: area under the curve).

To determine the association across strata and if the association differs across strata, a multinomial polytomous regression model with GOS-E at six months as the outcome, area under the curve, an indicator of stratum, and the two-way interaction as independent variables will be fit.

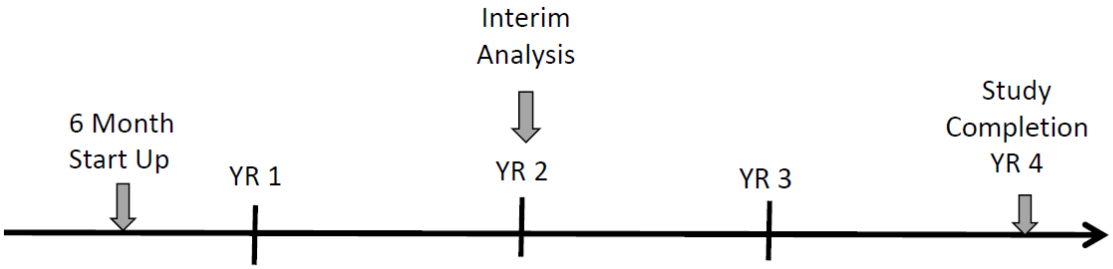
The same analytic approach will be used to measure outcomes at discharge except a hierarchical logistic regression model will be used.

Subgroup Analysis: The general approach to assess the homogeneity of a treatment effect across subgroup will be to include an interaction term between the treatment variable and the characteristics defining the subgroup in the regression model. A statistically significant interaction term would indicate that the null hypothesis of a homogenous effect would be rejected indicating a differential effect of the treatment across the subgroups. For example, when examining the homogeneity of the effect of whole blood on the primary outcome among those with and without a traumatic brain injury, the hierarchical logistic model will be modified to include a main effect for traumatic brain injury and the two-way interaction between whole blood use and traumatic brain injury.

Interim Analysis: There will be two aspects of the interim analysis. First, for efficacy, the Lan and Demets approach will be utilized to conduct the interim efficacy analysis. This approach is preferable over other approaches because it is flexible to the number of interim analyses conducted during the course of the study. The Lan and DeMets approach requires the use of a spending function to allocate the type I error to the interim analysis. The O'Brien and Fleming spending function which minimizes the type I error allocated to the interim analysis, saving the vast majority for the primary analyses will be used. For the proposed interim analysis, assuming that 50% of the study will be completed, it is estimated that the type I error allocated to the interim analysis will be 0.005, leaving 0.048 of the type I error for the primary outcome analysis.

Task Order 2: Shock, Whole blood and Assessment of TBI (SWAT)

Time Line: The study will occur over a 4 year period with a 6 month start up period, an interim analysis at 2 years and a 3.5 year enrollment period.



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