C. Clinical Protocol

University of Pittsburgh

Departments of Critical Care, Surgery and Emergency Medicine
MACRO (Multidisciplinary Acute Care Research Organization)

Study of Tranexamic acid during Air and ground Medical Prehospital transport (STAAMP) trial
Phase 3 Multi-center, Prospective, Randomized, Blinded, Controlled Interventional Trial
Protocol Version 2.7 date: January 11, 2019

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PROTOCOL SYNOPSIS

Study of Tranexamic acid during Air and ground Medical Prehospital transport (STAAMP) trial
PI – Jason L. Sperry MD, MPH, Co-PI- Frank X. Guyette MD, MS, MPH

Background: Traumatically injured patients continue to be plagued with uncontrolled hemorrhage resulting in significant morbidity and early mortality. A primary driving force for this unbridled hemorrhage is known to be the early coagulopathy which complicates severe injury. Trauma induced coagulopathy has been postulated to be an equilibrium imbalance between pro and anticoagulant factors, platelets, endothelium and fibrinolysis soon after injury. Recent evidence demonstrates that the early use of the antifibrinolytic agent tranexamic acid (TXA) after trauma center arrival results in improved survival in patients at risk for bleeding. Bringing this proven treatment to the prehospital arena and intervening earlier in those patients who would otherwise not be candidates for treatment has the real potential to further reduce or prevent the vicious hemorrhagic cascade, improve clinical outcomes and provide insight into the underlying mechanisms responsible for and which maximize its benefit.

Objective/Hypothesis: The primary hypothesis will be that prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of 30 day mortality. The secondary hypotheses include that prehospital tranexamic acid will reduce the incidence of hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism and early resuscitation needs, reduce or prevent the early coagulopathy as demonstrated by improving presenting INR and rapid thromboelastography parameters, reduce the early inflammatory response, plasmin levels, leukocyte, platelet and complement activation, and determine the optimal dosing of tranexamic acid post-injury.

Specific Aims:

Aim#1: Determine whether prehospital tranexamic acid as compared to placebo results in a lower incidence of 30 day mortality, 24 hour mortality, acute lung injury, multiple organ failure, nosocomial infection and improved shock parameters and early resuscitation and transfusion requirements.

Aim#2: Determine whether prehospital tranexamic acid as compared to placebo reduces hyperfibrinolysis, lowers the incidence of acute traumatic coagulopathy and improves early markers of coagulopathy.

Aim#3: To explore novel mechanisms by which prehospital tranexamic acid alters the inflammatory response independent of effects on hyperfibrinolysis including analysis of platelet and leukocyte activation, plasmin levels and plasmin mediated complement activation and the early cytokine response to trauma.

Aim#4: Determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, coagulopathy, clinical outcomes and the early inflammatory response.

Study Design: Multi-center, prospective, randomized, blinded, controlled interventional trial over 3 years focusing on patients with concern for bleeding who are transported via emergency medical transport to definitive care.

Population: Blunt or penetrating injured patients transported via emergency medical transport within two hours of estimated time of injury with concern for bleeding with 1.) a documented systolic blood pressure < 90 mmHg at the scene, en route, or at outside/referral facility OR 2.) documented tachycardia (> 110 bpm) at the scene, en route, or at outside/referral facility. Stage 1 Intervention: 1gm of tranexamic acid or placebo will be infused in a 100ml saline bag by emergency medical staff over approximately 10 minutes once inclusion criteria are met. Prehospital providers and trauma center arrival staff will be blinded to the treatment given. Stage 2 Intervention: After arrival enrolled patients who received tranexamic acid will undergo a second randomization to one of three different arms: 1.) repeat tranexamic acid dosing, 2.) standard dosing or 3.) abbreviated dosing. Placebo infusion bags will be used for blinding in all arms including those who received placebo for the Stage 1 Intervention. Patients and all treatment staff will be blinded to the intervention arm given for both stages. Randomization: Predetermined randomized allocation sequences using block sizes of 8 and 9 respectively for stage 1 and stage 2 interventions will be utilized.

Relevance: Few interventions exist that alter the morbidity and mortality that inherently follows traumatic injury. By extrapolating the beneficial effects of tranexamic acid found in the hospital to the prehospital setting will allow intervention at an earlier point promoting a cascade of consequences with positive effects, in a cohort

of patients who otherwise would not benefit due to the early administration requirement for tranexamic acid. The results provided by the successful completion of this proposal will have paramount implications for both civilian and military injured patients as control of coagulopathy and hemorrhage and delay to definitive care represent major impediments. The current proposal will add needed understanding and insight into improving outcomes when these impediments exist and will promote focus on the mechanisms responsible and the dosing requirements of tranexamic acid that maximize its benefit.

CLINICAL PROTOCOL

A. Statement of Work

Principal Investigators (PIs): Dr. Jason L. Sperry and Dr. Frank X. Guyette will oversee all planning and execution of the Study of Tranexamic acid during Air Medical Prehospital transport (STAAMP) trial which is a 3 year, multi-center, randomized, double blinded, placebo controlled clinical trial. For patients at risk of bleeding who are transported by emergency medical transport, a 1 gram bolus of prehospital tranexamic acid and subsequent in hospital tranexamic acid dosing regimens will be compared to placebo for clinical, coagulation, inflammatory and dosing regimen endpoints.

Coordinating Center: The University of Pittsburgh will be both the clinical outcome and data coordinating center. The University of Pittsburgh under the auspices of the Principal Investigators will be responsible for the education and training of participating center research staff and will oversee education and training of prehospital providers and research staff for participating centers. The University of Pittsburgh under the auspices of the Principal Investigators will be responsible for sample acquisition, sample storage, data acquisition and entry via web based platform, and maintenance of data integrity.

Participating Centers: Site Investigators from participating centers will oversee the planning and execution of the trial at their respective centers.

The Principal Investigators, the University of Pittsburgh and participating centers will thru the execution of the trial:

1. Determine whether prehospital tranexamic acid as compared to placebo reduces 30 day mortality, reduces the incidence of hyperfibrinolysis, Acute Traumatic Coagulopathy and improves early markers of coagulopathy and hyperfibrinolysis. (r-TEG parameters, D-dimers, activated protein C, and plasmin-anti-plasmin complexes)
2. Determine whether prehospital tranexamic acid as compared to placebo results in a lower incidence of 24 hour mortality, acute lung injury, multiple organ failure, nosocomial infection, shock parameters, early resuscitation and transfusion needs, early seizures and pulmonary embolism.
3. To explore potential novel mechanisms by which tranexamic acid alters the inflammatory response to injury independent of effects on hyperfibrinolysis including effects on platelet and leukocyte activation via flow cytometry, measurements of plasmin levels and subsequent plasmin mediated complement activation and the early inflammatory cytokine response to trauma.
4. Determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, markers of coagulopathy, clinical outcomes, and the early inflammatory response.

Pre Trial Start Period: The PIs and Site investigators will obtain FDA approval followed by approval for exception from consent for emergency research from their respective IRBs. The University of Pittsburgh as coordinating center will create a web based data entry platform for the trial.

Year 1: Following a 1 month training period for participating centers on enrollment procedures and TEG analysis, trial enrollment will begin with an estimated 330 patients enrolled by years end. Blood samples will be batched for plate assay analysis at the University of Pittsburgh and prospective outcomes data will be obtained,

entered and integrity verified. First interim analysis will occur at 1/3 of total patient enrollment. Those exploratory aim measurements that require fresh blood samples will occur at the University of Pittsburgh alone.

Year 2: An estimated additional 330 patients will be enrolled (total=660) by end of the second year and blood samples will again be batch analyzed for plate assay analysis. Continued prospective data collection and integrity verification for clinical outcomes will occur. A second interim analysis will occur after 2/3 of total patient enrollment. Exploratory aim measurements which require fresh blood samples will occur at the University of Pittsburgh alone.

Year 3: An estimated additional 334 patients will be enrolled (total=994) by end of third year, blood samples will be batched for analysis. Continued prospective data collection and integrity verification for clinical outcomes will occur. Exploratory aim measurements which require fresh blood samples will occur at the University of Pittsburgh alone. Study completion, final manuscript preparation will soon follow.

B. Investigators

Principal Investigator:	**Jason L. Sperry MD, MPH**, Associate Professor of Surgery and Critical Care Medicine, Co-Director of Acute Care Fellowship, University of Pittsburgh

Sub-Investigators and Key Study Personnel:

Co-Investigators:	**Frank X. Guyette MD, MS, MPH**; **Brian S. Zuckerbraun MD; Clifton Callaway, MD, PhD; Graciela Bauza, MD; Raquel Forsythe, MD; Juan C. Puyana, MD; Gregory Watson, MD; Ankur Doshi, MD; Scott Gunn, MD; Christian Martin-Gill, MD; Paul Phrampus, MD; Matthew Rosengart, MD; Matthew Neal, MD; Barbara Early, RN, BSN, Adam Janicki, MD; Joseph Yanta, MD; Adam Frisch, MD; Aaron Brown, MD; Anthony Pizon, MD; Joshua Shulman, MD; Adam Tobias, MD, MPH; Julie McCausland, MD; Alexandra Castro, MD; Charissa Pacella, MD; Amy Talley, MD; Ross McCormack, MD**
Consultant:	**Mazen Zenati MD, MPH, PhD,** Assistant Professor of Surgery and Epidemiology, University of Pittsburgh
Consultant:	**Derek C. Angus MD, MPH,** The Mitchell P. Fink Professor and Chair, Department of Critical Care Medicine, University of Pittsburgh
Consultant:	**Timothy R. Billiar MD,** George Vance Foster Professor and Chair, Department of Surgery, University of Pittsburgh
Consultant:	**Alan D. Murdock MD,** Chief of Acute Care Surgery, Department of Surgery, University of Pittsburgh, Consultant to the Surgeon General for Trauma/Critical Care, Air Force Medical Operations Agency
Consultant:	**Andrew B. Peitzman MD,** Mark M. Ravitch Professor and Vice-Chair, Chief, Division of General Surgery, University of Pittsburgh
Research Monitor:	**Louis Alarcon, MD**, Medical Director, Trauma Surgery; Associate Professor of Surgery and Critical Care, University of Pittsburgh

Collaborating Centers and Site Principal Investigators:

University of Arizona:	**Gary Vercruysse, MD,** Medical Director, Burn Care Program, Associate Professor of Surgery, University of Arizona
University of Texas, San Antonio:	**Brian J. Eastridge MD,** Chief of Trauma Services, Professor-Clinical, Department of Surgery, University of Texas at San Antonio
University of Utah:	**Raminder Nirula MD, MPH,** Associate Professor of Surgery, Surgical Critical Care Fellowship Director, University of Utah

C. Background and Significance

C.1. Uncontrolled hemorrhage and coagulopathy remain leading causes of mortality post-injury: Hemorrhage is estimated to be responsible for over 40% of all trauma-related deaths, nearly half of which occur in the pre-hospital setting.[1,2] Uncontrolled bleeding remains the leading cause of early in hospital mortality.[3,4] Ongoing hemorrhage is complicated by the well-known 'lethal triad' of coagulopathy, hypothermia and acidosis (**Fig 1**.).[5-8] It has been demonstrated that persistent hypothermia and progressive metabolic acidosis are associated with severe recalcitrant coagulopathy and resultant unbridled hemorrhage.[9-12] Although multiple mechanisms which promote or result in coagulopathy post-injury have been proposed and studied, interventions that reduce the morbidity and mortality associated with hemorrhage and coagulopathy in the clinical arena remain limited.[13,14]

C.2. Coagulopathy occurs early and is a complex, primary process following injury: Coagulopathy has been shown to be present in over 25% of patients at the time of trauma admission and has been determined to be an independent predictor of mortality with an associated 4-fold higher risk of mortality in both civilian and military settings.[15-19] Those injured who arrive with coagulopathy also have been shown to have longer ICU stays and ventilator requirements, are more likely to develop acute renal injury, multiple organ failure, and have a trend towards a greater incidence of acute lung injury.[18,20] Prior literature has suggested that the coagulopathy which complicates injury is a secondary event driven by physiologic derangements and abnormalities.[7,9,21,22] Evolving evidence suggests that these prior mechanisms individually, which drive dysfunction or consumption of coagulation factors, may be too simplistic.[23] More recent evidence demonstrates the importance of shock and tissue hypoperfusion as principle drivers of coagulopathy following injury which results in an imbalance of the equilibrium between procoagulant factors, anticoagulation factors, platelet and leukocyte activation, and fibrinolysis.[12,20,23-26] (**Fig 2**.) As our understanding has increased regarding the mechanisms responsible for the acute coagulopathy of trauma, a new paradigm where early coagulopathy post-injury is considered a complex, multi-factorial, primary event has developed.[22,23,27]

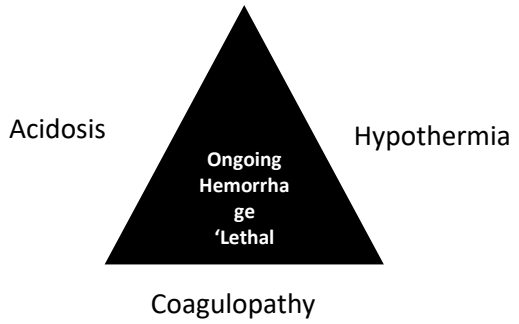


Fig 1. Adapted from Jansen JO, et al. BMJ. 2009 Jun 5;338:b1778

It is with this understanding that the scope and magnitude of morbidity due to uncontrolled hemorrhage is demonstrated, highlighting the importance of the potential benefits of prehospital tranexamic acid which may have a greatly magnified effect by intervening during the earliest time period and in those patients who would otherwise not be candidates for treatment due to the early time requirements for its administration .

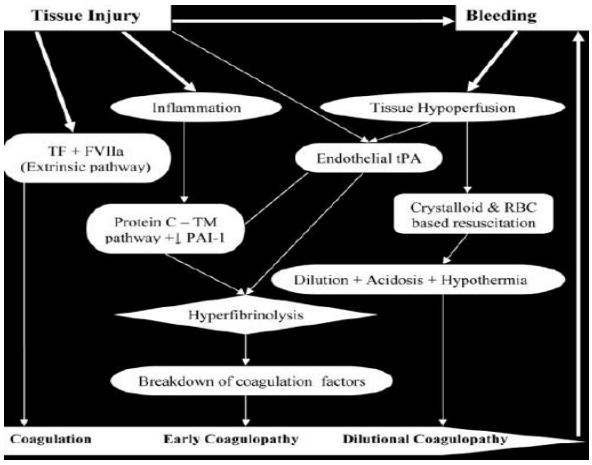


Fig 2. Nascimento B. et al. Crit Care. 2010; 14(1): 202.

C.3. Hyperfibrinolysis is associated with poor outcome following traumatic injury: Hyperfibrinolysis has been identified as an integral component of acute traumatic coagulopathy.[28,29] The incidence of hyperfibrinolysis as measured by thromboelastography (TEG) has been identified in 2% to 34% of trauma patients, with those patients who require large volume transfusion (>10 units in first 6 hours) having the highest incidence.[29-31] It has been shown to occur early, following traumatic injury and significantly associated with an independent greater risk of mortality, the need for massive transfusion, higher injury and shock severity, and greater prehospital crystalloid resuscitation.[29-32] Importantly, recent evidence suggests moderate fibrinolysis, as measured by elevated plasmin-antiplasmin complexes in serum, may be apparent in over 50% of patients.[32] This more common, subclinical measurement of fibrinolytic activity is not able to be assessed using standard TEG analysis, but is associated again with significantly greater 28-day mortality, greater ICU requirements and longer length of stay.

C.4. Rapid-thromboelastography (TEG) and hyperfibrinolysis: As we continue to expand our understanding of the acute coagulopathy of trauma, emphasis has also been placed on diagnosing coagulopathy which complicates injury to allow real time assessment to guide evolving blood component transfusion requirements.[33] Increasing evidence suggests that historic reliance on prothrombin time (PT), and international normalized ratio (INR) is time exclusive and provides insufficient information relative to the complexity which drives this coagulopathic process.[34-36] Needed for the appropriate evaluation of an acutely injured patient's coagulation status is a rapid, reliable assessment of the thrombosis and fibrinolysis arms of the hemostatic cascade. Thromboelastography (TEG) is a technology which provides a real time, viscoelastic analysis of these blood clotting processes.[33] (**Fig 3**.) Point-of-care rapid thromboelastography (POC r-TEG) differs from standard TEG because the clotting process and subsequent analysis is accelerated by the addition of tissue factor to a whole blood sample.[37] POC r-TEG is limited, however, by the requirement that the analysis be performed within minutes of blood draw to prevent clot formation unless the addition of citrate occurs.[37] It has been demonstrated the TEG can assess coagulopathy, platelet dysfunction and most importantly, hyperfibrinolysis at an early stage following injury and is the most rapid available test for providing reliable information on coagulopathy in significantly injured patients.[38,39] If not more important, the technology has been deemed feasible for use in a deployed military setting as well as for civilian use.[40]

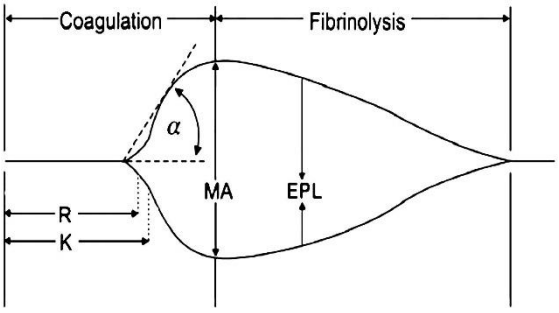


Fig 3. Standard TEG parameters. Reaction (R) time, clot formation (K) time, fibrin cross-linking (angle = α), clot strength (maximal amplitude [MA]), and estimated percent lysis (EPL). Harr JN,et al. J Surg Res. 2011 Oct;170(2):319-24.

C.5. Early tranexamic acid reduces mortality post-injury:

In a large, civilian, multicenter, randomized, controlled trial (CRASH-2 trial) on the use of tranexamic acid in patients at risk of bleeding, a significant reduction in mortality was found with its use.[41] Tranexamic acid is a lysine analog that is known to interfere with binding sites on plasminogen and inhibit fibrinolysis.[42] Inclusion criteria for the trial included hypotension SBP <90 mm Hg or tachycardia (> 110 beats per min), in patients at risk of significant hemorrhage within 8 hours from injury. Dosing of tranexamic acid was given in a bolus 1 gram dose over approximately 10 minutes followed by an infusion dose (additional 1 gram) over eight hours. This therapy was subsequently found in exploratory analysis to be beneficial in those who received tranexamic acid in the first 3 hours from injury and strongest in those patients who received it in the first hour following injury.[43] Pre-specified analysis of the trial data demonstrated that the mortality benefit attributable to tranexamic

acid remained consistent across patients with low thru high predicted mortality in those enrolled in the first 3 hours from injury, suggesting its use should not be limited to the most severely injured.[44] Importantly, subgroup analysis on patients with brain injury revealed neither moderate benefits nor moderate detrimental effects and provides grounds for further evaluation in those patients with traumatic brain injury.[45] Military experience with tranexamic also has demonstrated beneficial effects in a large retrospective analysis (MATTERs) study.[46] The use of tranexamic acid within 1 hour of injury was associated with a lower mortality despite higher injury severity, and a lower incidence of coagulopathy as measured by standard laboratory testing (prothrombin time or activated partial thromboplastin time). Importantly, no information regarding the potential benefits of pre-hospital tranexamic acid currently exists.

C.6. Mechanisms responsible for the beneficial effects of tranexamic acid following injury remain inadequately characterized: Tranexamic acid is known to inhibit fibrinolysis and has most commonly been used to decrease blood loss during cardiac and orthopedic surgeries.[47-50] Its hypothetical benefit following traumatic injury would be derived from reducing blood loss and hyperfibrinolysis and the attributable independent morbidity associated with blood transfusion and coagulopathy. The CRASH-2 trial, despite showing a mortality benefit in over 20,000 enrolled patients, provides little insight into the mechanisms responsible for its beneficial effect.[41] Early coagulopathy measurements or TEG analysis to measure fibrinolysis were not performed while only 50% of enrolled patients required blood transfusion at all.[46] In the trial, total blood transfusion was recorded along with operative procedures, with neither of these important outcomes being different across treatment groups (tranexamic acid vs. placebo). Early blood transfusion requirements in the first 6 hour and 24 hours when tranexamic acid may have its greatest affect, were not recorded. In the retrospective military study (MATTERs) tranexamic acid was associated with greater 24 hour blood and blood component transfusion requirements and despite higher injury severity, the tranexamic acid group remained associated with lower mortality.[46] The current evidence suggest that in addition to altering fibrinolysis, tranexamic acid may also effect outcome via a non-antifibrinolytic mechanism.

The successful completion of the proposed aims of the current proposal will provide needed insight into the mechanisms responsible for the mortality benefit attributable to tranexamic acid in patients at risk for hemorrhage including those with brain injury, allowing focus on specific pathways and future therapeutic targets that will further improve care of the injured patient.

C.7. Plasmin and its pro-inflammatory effects: Tranexamic acid is a lysine analogue that interferes with binding of plasminogen to fibrin, which is required for plasmin activation.[42] Plasmin has pro-inflammatory effects by activating monocytes, neutrophils, platelets, endothelial and dendritic cells and induces pro-inflammatory genes.[51,52] Plasmin also induces chemotaxis of monocytes and dendritic cells and in-vitro and in-vivo studies have demonstrated the ability of plasmin to stimulate the production reactive oxygen species and promote the release of lipid mediators and cytokines via complement activation.[51,53] Tranexamic acid benefits in cardiac surgery have been hypothesized to be secondary to a reduction in the inflammatory response, possibly via a reduction of plasmin activation.[53-55] The mortality benefit associated with tranexamic acid may occur secondary to an anti-inflammatory effect due to a reduction in plasmin activation. (**Fig 4**.)

C.8. Safety and dosing of tranexamic acid: Tranexamic acid has been most commonly used in cardiac surgery and orthopedic surgery for its blood transfusion reduction effects with the risks of thrombotic complications and post-operative seizures being the most common complications reported with its use.[49,50,56,57] It has been retrospectively compared to other anti-fibrinolytics used in cardiac surgery and shown to have a similar or better safety profile in most studies. Post-operative seizures, due to a GABA receptor antagonist effect, have also been documented following cardiac surgery and this complication is thought to be a dose dependent effect.[58,59] An orthopedic meta-analysis demonstrated no higher risk of venous thromboembolism following hip and knee replacement, surgeries typically thought to be at increased risk of thromboembolism.[49] The literature does suggest that further higher level studies are

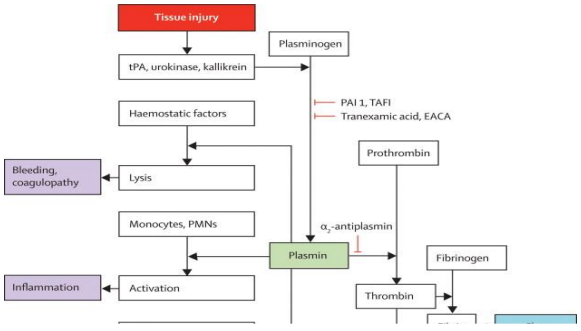


Fig 4. Pro-inflammatory and coagulation system effects of plasmin. Levy JH. Lancet. 2010 Jul 3;376(9734):3-4

required to verify the safety profile of lysine analogue anti-fibrinolytics in the non-injured patient population.[49,60] The CRASH-2 trial, which looked at over 20,000 patients demonstrated no differences in deaths from vascular occlusive events including myocardial infarction, stroke, and pulmonary embolism and concluded the tranexamic acid safely reduced the risk of death in bleeding trauma patients.[41] Importantly, the trial demonstrated that mortality due to bleeding was increased in patients who received tranexamic acid beyond 3 hours from injury.[43] In the retrospective military study (MATTERs, 896 patients) an increased incidence of deep vein thrombosis and pulmonary thromboembolism was demonstrated. These results were, however, confounded by higher injury severity in the tranexamic acid group.[46]

The dosages used in the trauma population studies have been 1 to 2 grams either in loading and/or infusion route, all within the first 8 hours from injury. For the CRASH-2 trial, the dosage regimen was selected to provide a fixed dose within the range shown to inhibit fibrinolysis in larger patients and safe in smaller patients (10 mg/kg loading and 1mg/kg/hr infusion dose).[41] For the military MATTERs study, 1 gram of tranexamic acid was given as a loading dose with the potential for repeat loading dosages.[46] Based upon these prior studies, the most safe and optimal dosing regimen in trauma patients at risk for bleeding remains obscure.[60]

C.9. Delay to definitive hemorrhage control: Definitive control of ongoing hemorrhage remains a fundamental principle in trauma management. Increasing attention has been paid to the significance of delay and the timing of definitive control of hemorrhage. Clarke and colleagues have previously shown that delays to operative intervention in patients with significant abdominal injuries are associated with a higher mortality risk, demonstrating a 1% higher risk of mortality for every 3 minute delay in getting patients from the ED to laparotomy.[61] Additional studies documenting relationships between delay and poor outcome following injury have been demonstrated for interventional radiology procedures and by excessive radiographic imaging post-injury in the hospital setting.[62,63] Prehospital air medical transport has been shown to be associated with improved outcome following severe injury, however, scene time and overall transport times are consistently longer as compared to ground transportation in both civilian and military setting.[64-68]

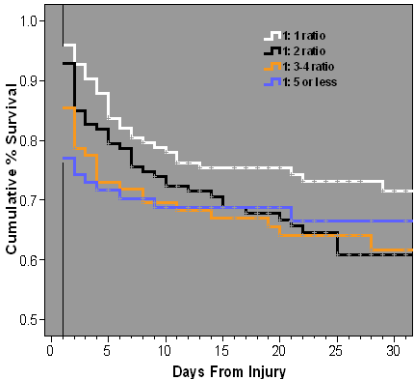


Fig 5. Kaplan-Meier Survival Analysis comparing survival across different transfusion ratio groups.

The results provided by the successful completion of this proposal will have paramount implications for both civilian and military injured patients as control of hemorrhage and delay to definitive care represent major impediments for both populations. This proposal will provide needed insight into the consequences of early tranexamic acid intervention following injury, the mechanisms responsible for its beneficial effects and the dosage regimen that maximizes its benefit when these impediments exist.

D. Preliminary Studies

D.1. Addressing coagulopathy is associated with improved survival and reduction in blood transfusion requirements: Secondary to the University of Pittsburgh's participation with the *Inflammation and the Host Response to Injury Large Scale Collaborative Program* prospective cohort trial, *(www.gluegrant.org)*, we have previously characterized the relationships of addressing the early coagulopathy following acute injury and the outcomes associated with its presence.[69-74] We have documented the relationship between high fresh frozen plasma:packed red blood cell (FFP:PRBC) transfusion ratios in

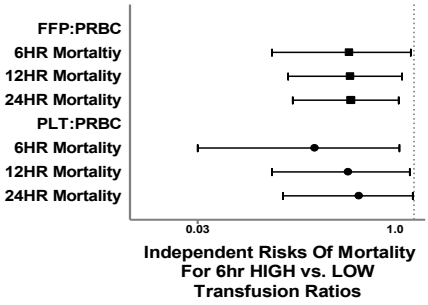


Fig 7. Mortality risks for 6hr High and Low transfusion ratios over the first 24hrs post injury.

	High F:P (n = 102)	Low F:P (n = 313)	p
12 h Postinjury			
Blood (unit)	14.3 ± 7	20.5 ± 15	0.001*
Fresh frozen plasma (unit)	14.0 ± 7	6.8 ± 7	0.001*
Crystalloid (L)	15.5 ± 7	15.3 ± 8	0.798
Platelet (unit)	1.4 ± 1	1.3 ± 2	0.744
Cryoprecipitate (unit)	3.2 ± 4	2.0 ± 4	0.006*
24 h Postinjury			
Blood (unit)	16.0 ± 9	22.0 ± 17	0.001*
Fresh frozen plasma (unit)	15.2 ± 9	7.6 ± 9	0.001*
Crystalloid (L)	18.8 ± 9	18.7 ± 11	0.892
Platelet (unit)	1.8 ± 2	1.6 ± 2	0.525
Cryoprecipitate (unit)	3.3 ± 4	2.3 ± 4	0.030*

Fig 6. Transfusion requirements across High and Low FFP:PRBCs groups

massive transfusion patients and outcome.[74] We verified a dose response relationship revealing as the FFP:PRBC increased toward 1:1.5, a significant reduction in mortality occurred. (**Fig 5**.) Equally important, there were significant reductions in blood and blood component transfusion requirements in those with High vs. Low FFP:PRBC transfusion ratios. (**Fig 6**.) More recent analyses aimed to debunk any question of survival bias regarding high plasma transfusion ratios in the glue grant cohort.[71] Cox-Hazard regression was used to determine the independent mortality risks at 6hr, 12hr, and 24hrs while controlling for important confounders. FFP:PRBC and platelet:PRBC ratios were also analyzed as time-dependent covariates accounting for fluctuation over time. We found that despite similar degrees of early shock and coagulopathy, HIGH FFP:PRBC and platelet:PRBC ratios are associated with a survival benefit as early as 6hrs and throughout the first 24hrs, even when time dependent fluctuations of component transfusion were accounted for. (**Fig 7.)** We concluded that the observed mortality benefit associated with high component transfusion ratios was unlikely due to survivor bias and that early attainment of high transfusion ratios may significantly lower the risk of mortality in MT patients. *This prior work demonstrates that addressing the coagulopathy following significant injury is associated with improved outcome.*

D.2. Early attention to coagulopathy is associated with a reduction in massive transfusion: We have recently characterized changes in resuscitation practice which have occurred over time in a cohort severely injured patients requiring massive transfusion.[73] We demonstrated that the incidence of massive transfusion (>10 units blood) significantly decreased over time, despite the median ISS of the cohort increasing. (**Fig 8**.) When the recent period (2007-current) was compared to the early time period (2004-2006) of enrollment for the study, there was a significant increase in the FFP:PRBC and platelet:PRBC transfusion ratios as early as 6 hours post injury, and the proportion of each blood component that was given in first 6hrs relative to the total give at 24 hours significantly increased. (**Fig. 9**.) This occurred in patients who required 7-10 units of blood, just below the definition of massive transfusion. The data suggests that early, more aggressive attainment of high transfusions ratios may reduce the requirement for massive transfusion and may shift overall blood requirements below those which currently define massive transfusion. *This previous work suggests that early attention to coagulopathy is associated with improved outcome, highlighting the importance of prehospital interventions known to have a beneficial effect.*

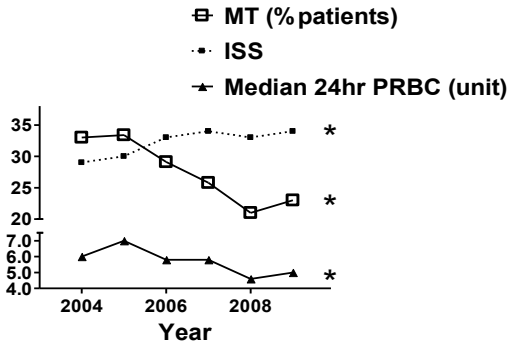


Fig 8. Decreasing incidence of massive transfusion over time with increasing injury severity

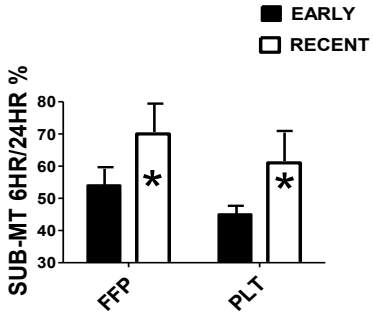


Fig 9. Comparing the proportion of component transfusion in the first 6 hours relative to 24 hours in early and recent time periods.

D.3. Prehospital interventions and management practice are associated with outcome differences following traumatic injury: Secondary to the University of Pittsburgh's participation with the *Resuscitation Outcomes Consortium* (https://roc.uwctc.org/), prior work has demonstrated the importance of interventions in the prehospital arena.[75-79] We have also previously demonstrated the expertise the air medical service has with air medical interventions in injured patients.[80-82] A recent analysis demonstrates the importance of prehospital serum lactate measurement during air medical transport for traumatic injury and its role as an independent predictor of in-hospital death, need for emergent operative intervention and the

	Odds Ratio (95% CI)
Predictor for in-hospital death	
Serum lactate concentration	1.23 (1.14–1.34)
Initial heart rate (bpm)	0.97 (0.96–0.98)
GCS score <15, n(%)	7.03 (3.8–13.0)
Predictor for emergent operation	
Serum lactate concentration	1.13 (1.05–1.21)
Initial systolic blood pressure	0.98 (0.97–0.99)
Predictor for MODS	
Serum lactate concentration	1.14 (1.03–1.23)
Age (yr)	1.05 (1.01–1.08)

Fig 10. Logistic regression results for prehospital lactate predicting risks for in-hospital death, need for emergent operation and multiple organ failure.

development of multiple organ failure.[83] (**Figure 10.**) More recent work demonstrates the utility of air medical tissue oximetry and the ability it has to predict operative intervention or blood transfusion in the first 24 hours following injury.[84] (**Figure 11**.) A recent study which was presented at the 2012 AAST annual meeting utilizing Gluegrant dataset demonstrated that overly aggressive prehospital crystalloid use was associated with an independent greater risk of early coagulopathy and mortality in patients who were normotensive (SBP> 90mmHg) while a trend towards benefit and lower risks of poor outcome were found in patients with prehospital hypotension (SBP<90mmHg). (Journal of Trauma and Acute Care Surgery. *In Press*, 2013, **Figure 12**.)

D.4. Feasibility of the trial: The collaborative environment between the Departments of Surgery and Emergency Medicine at the University of Pittsburgh unifies prehospital clinical research expertise with hospital based acute care research expertise and will provide the main impetus for the successful execution of the current proposal. The principal investigators participation and involvement in the Inflammation and the Host Response to Injury Program, (Glue grant), the Resuscitation Outcomes Consortium (ROC) and recent funding (proposal #11152002, W81XWH-12-2-0023) from the Department of Army for the 'Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH) Program' documents and verifies the robust nature of the University of Pittsburgh's multi-center research collaborations and expertise in prehospital investigations, the clinical research infrastructure that is available and the institutional and departmental support to promote and allow the successful execution and completion of the proposed aims that will provide important knowledge into the mechanisms and appropriate dosing of tranexamic acid that maximize its beneficial effects.

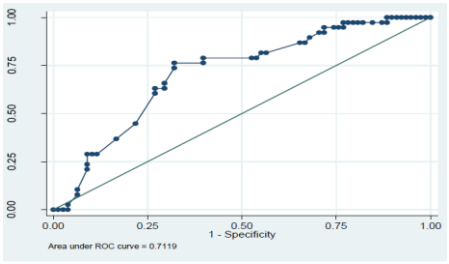


Fig 11. ROC curve revealing ability of prehospital tissue oximetry to predict operative intervention or blood transfusion in first 24 hours post-injury

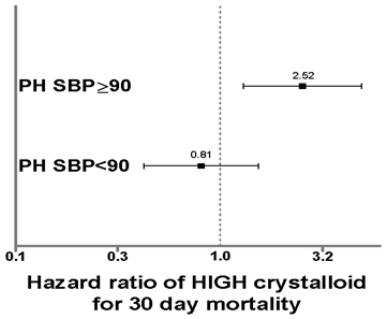


Fig 12. Forest plot depicting independent mortality risks associated with high volume prehospital crystalloid in hypotensive and non-hypotensive

D.5. Feasibility of air medical service intervention at the University of Pittsburgh: Under the direction of Dr. Frank Guyette, Co-Principal Investigator of this proposal, the air medical service at the University of Pittsburgh is the busiest non-profit flight service in the country and has a significant track record of prospective trials and interventions in the prehospital arena.[76,78,79,82-86] **The air medical service at the University of Pittsburgh has 14 air medical bases which have flown over 1,600 injured patients to Presbyterian Hospital, the busiest level 1 trauma center in the state of Pennsylvania, over the last 12 months (2012 data). The DOD funded PAMPer trial (Prehospital Air Medical Plasma trial) under the auspices of the PUPTH Program will utilize only 4 out of the 14 air medical bases which reside closest to blood banking affiliates due to the requirement of thawed plasma for the multi-center trial. The remaining 10 helicopter bases will be utilized for the current proposal providing one of largest patient populations available across the country for an air medical prehospital intervention.** It is this extensive prehospital investigation expertise and experience that will promote and allow the successful completion of the aims of the proposal.

D.6. Clinical research infrastructure and coordinating center expertise of the University of Pittsburgh: The Department of Surgery at the University of Pittsburgh has interdepartmental research affiliations with the Department of Critical Care Medicine and the Department of Emergency Medicine and has spearheaded the Multidisciplinary Acute Care Clinical Research Organization (MACRO). MACRO is a unique, interdepartmental resource with laboratory facilities, an experienced and professionally-trained staff of 11 clinical research coordinators, 15 research associates and 24 hour around the clock screening capabilities. They have extensive experience with data entry, multi-center data coordination, training, IRB liaison needs, web-based data entry platform creation and specimen management and storage. MACRO follows a cost center model and provides 'cost-neutral' services to clinical investigators from diverse specialties in order to conduct clinical and translational research. Currently, Over 71 principal investigators and co-investigators from 9 different departments currently utilize MACRO services. Thru 2012 alone, MACRO's services were utilized for 14

interventional trials and 11 observational trials. MACRO has been the clinical research infrastructure utilized for the institutions involvement in the *Gluegrant* and *ROC* studies and is the infrastructure that is being utilized for the multi-center coordination of the DOD funded PAMPer trial. It is with the dedicated clinical research infrastructure provided by MACRO at the University of Pittsburgh that the aims of the current proposal can successfully be completed.

D.7. Feasibility of patient recruitment for the trial: As demonstrated by being essential participants of both the *Gluegrant* and *ROC* studies*,* the departments of Surgery and Emergency Medicine at the University of Pittsburgh have a significant track record of successful patient recruitment and enrollment in large prehospital and in hospital prospective trials for traumatic injury. Regarding the specifics of the current proposal, over the last 12 months, the air medical services that will be utilized for this trial has transported > **150 patients** meeting the specific inclusion and exclusion criteria for this proposal (SBP < 90mmHg and tachycardia - > 110 bpm). Participating centers have been chosen with similarly busy air medical services and with a history of involvement with the Gluegrant, ROC or with other multi-institutional clinical research experience*. It is under the auspices of the collaborative clinical research environment of the University of Pittsburgh and these busy participating trauma centers that the specific objectives and aims of the current proposal can successfully be accomplished.*

E. Objectives/Hypotheses

E.1. Study Rationale: Traumatic injured patients continue to be plagued with uncontrolled hemorrhage resulting in significant morbidity and early mortality. A primary driving force for this unbridled hemorrhage is known to be the early coagulopathy which complicates severe injury. Trauma induced coagulopathy has been postulated to be an equilibrium imbalance between pro and anticoagulant factors, platelets, endothelium and fibrinolysis soon after injury. Recent evidence demonstrates that the early use of the antifibrinolytic agent tranexamic acid after trauma center arrival results in improved survival in patients at risk for bleeding. Bringing this proven treatment to the prehospital arena and intervening earlier in those patients who would otherwise not be candidates for treatment has the real potential to further reduce or prevent the vicious hemorrhagic cascade, improve clinical outcomes and provide insight into the underlying mechanisms responsible for and which maximize its benefit.

E.2. Primary Objective: To determine the effect of prehospital tranexamic acid infusion (1 gram over approximately 10 minutes) as compared to placebo during emergency medical transport in patients at risk of traumatic hemorrhage on 30 day mortality.

E.2.1. Primary Aim#1: Determine whether prehospital tranexamic acid as compared to placebo reduces 30 day mortality in patients at risk for traumatic hemorrhage.

***Primary Hypothesis 1*:** Prehospital tranexamic acid as compared to placebo will reduce 30 day mortality in patients at risk of traumatic hemorrhage

E.3. Secondary Objectives: To determine the effect of prehospital tranexamic acid infusion (1 gram over approximately 10 minutes) as compared to placebo during emergency medical transport in patients at risk of traumatic hemorrhage on the incidence of hyperfibrinolysis (estimated percent lysis > 7.5%, first 30 minutes by rapid-thromboelastography) acute traumatic coagulopathy (ATC), early markers of coagulopathy, the incidence of 24 hour mortality, acute lung injury, multiple organ failure and development of nosocomial infection, shock parameters and resuscitation/transfusion requirements, platelet and leukocyte activation and the early inflammatory response and to determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, coagulopathy, clinical outcomes and the early inflammatory response.

E3.1. Secondary Aim#1: Determine whether prehospital tranexamic acid as compared to placebo reduces the incidence of hyperfibrinolysis (estimated percent lysis > 7.5%), acute traumatic coagulopathy (ATC, presenting INR > 1.4), improves PT measurements and additional r-TEG parameters, D-dimer levels, activated Protein C levels, and plasmin-antiplasmin complexes.

Secondary Hypothesis 1: Prehospital tranexamic acid as compared to placebo will reduce the incidence hyperfibrinolysis (estimated percent lysis > 7.5%), reduce the incidence of patients with an arrival INR > 1.4, improve PT and additional presenting r-TEG parameters of coagulopathy including ACT, r-value, k-time, α-angle, maximal amplitude (MA) and G-values and D-dimer levels, activated Protein C levels and plasmin-antiplasmin complexes.

E.3.2. **Secondary Aim#2**: Determine whether prehospital tranexamic acid as compared to placebo results in a lower incidence of 24 hour mortality, acute lung injury, multiple organ failure, nosocomial infection, early seizures, pulmonary embolism, shock parameters and early resuscitation and transfusion requirements.

Secondary Hypothesis 2A: Prehospital tranexamic acid as compared to placebo will reduce the incidence of 24 hour and 30 day mortality, acute lung injury, multiple organ failure, nosocomial infection, early (24hr) seizures and in-hospital pulmonary embolism.

Secondary Hypothesis 2B: Prehospital tranexamic acid as compared to placebo will improve presenting base deficit, 24 hour crystalloid requirements and reduce 6 hour and 24 hour blood and blood component transfusion requirements (PRBC, FFP and platelets).

E.3.3. Secondary Aim #3: To investigate potential novel mechanisms by which tranexamic acid alters the inflammatory response to injury independent of effects on hyperfibrinolysis. Investigations of the effects of tranexamic acid on inflammation will include analysis of platelet and leukocyte activation via flow cytometry, measurements of plasmin levels and subsequent plasmin mediated complement activation and the early inflammatory cytokine response to trauma.

Secondary Hypothesis 3A: Prehospital tranexamic acid as compared to placebo will reduce plasmin levels and markers of platelet and leukocyte activation measured by flow cytometry (FACS) and result in a plasmin mediated reduction of complement activation as measured by C3a and Factor B levels.

Secondary Hypothesis 3B: Prehospital tranexamic acid as compared to placebo will attenuate trauma-induced pro-inflammatory changes and immunosuppression by reducing the early inflammatory cytokine response (GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10 and TNF-α), HMGB1 levels and early inflammatory gene responses as measured by RT-PCR.

E.3.4. Secondary Aim#4: Determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, markers of coagulopathy, clinical outcomes, platelet and leukocyte activation and the early inflammatory response.

***Secondary Hypothesis 4A*:** Repeat dosing of 1 gram of tranexamic acid followed by 1 gram over approximately 8 hours after hospital arrival in patients who have already received 1 gram of prehospital tranexamic acid will lower the incidence of 12 hour (from arrival) hyperfibrinolysis (estimated percent lysis > 7.5%), coagulopathy (INR > 1.4) and improve r-TEG markers of coagulopathy, D-dimer levels, activated protein C levels and plasmin-antiplasmin complex levels as compared to standard dosing of tranexamic acid (1 gram over approximately 8 hours) or abbreviated dosing (no additional tranexamic acid).

Secondary Hypothesis 4B: Repeat dosing of 1 gram of tranexamic acid followed by 1 gram over approximately 8 hours after hospital arrival in patients who already received prehospital tranexamic acid will lower the incidence of 24 hour and 30 day mortality, acute lung injury, multiple organ failure and nosocomial infection as compared to standard dosing or abbreviated dosing.

Secondary Hypothesis 4C: Repeat dosing of 1 gram of tranexamic acid followed by 1 gram over approximately 8 hours after hospital arrival in patients who already received prehospital tranexamic acid will reduce 12 hour (from arrival) base deficit, 24 hour crystalloid requirements and 6 hour and 24 hour blood and blood component transfusion requirements (PRBC, FFP and platelets) as compared to standard dosing or abbreviated dosing.

Secondary Hypothesis 4D: Repeat dosing of 1 gram of tranexamic acid followed by 1 gram over approximately 8 hours after hospital arrival in patients who already received prehospital tranexamic acid will reduce 12 hour and 24 hour (from arrival) markers for platelet and leukocyte activation, plasmin

levels, markers of complement activation, HMGB1 levels and the early inflammatory cytokine response as compared to standard dosing or abbreviated dosing.

F. Project Milestones:

The proposal is for a 3 year trial. The FDA approval process will be initiated after notification of proposal funding. Community notification and other procedures associated with exception from consent for emergency research will be initiated and completed prior to IRB approval at all institutions. Following final IRB approval a 1.5 month startup period will be utilized to verify and educate all centers prior to beginning enrollment. A data entry web based platform will be created during this same time period. Enrollment will occur for 33 months (2.75 years) with prospective data entry of laboratory and TEG measurements, clinical outcomes, transfusion requirements and demographic and injury characteristics. Serum for cytokine and ELISA measurements will be batched and sent to the University of Pittsburgh on an annual basis. We expect approximately 70 patients per year per institution on average. Flow cytometry for platelet and leukocyte activation and RT-PCR may be performed at the University of Pittsburgh prospectively on a subset of patient samples. Enrollment will be monitored on a semi-annual basis for each participating center. Data safety and monitoring over the course of the clinical trial will fall under the responsibility of an independent data safety and monitoring board (DSMB). Interim analysis will occur at 33% and 66% of patient enrollment. A 1.5 month data cleaning and wind down will occur once enrollment has been completed, allowing data analysis and manuscript preparation.

G. Military Significance/Public Purpose:

Despite the significant advances in trauma care delivery and post-injury management practices which have occurred over the last decade, uncontrolled hemorrhage remains one of the leading causes of trauma related deaths.[4,5,87,88] Recent evidence demonstrates that the early use of the antifibrinolytic agent tranexamic acid after trauma center arrival results in improved survival in patients at risk for bleeding.[41] Bringing this proven treatment to the prehospital arena and intervening earlier in those patients who would otherwise not be candidates for treatment has the real potential to further reduce or prevent the vicious hemorrhagic cascade, improve clinical outcomes and provide insight into the underlying mechanisms responsible for and which maximize its benefit. This potential knowledge base would be dramatically beneficial to both military and civilian trauma systems. It is in both these settings where the prehospital phase of treatment represents a relatively novel arena for new interventions. The results provided by the successful completion of this proposal will have paramount implications for both military and civilian injured patients as control of hemorrhage and delay to definitive care represent major impediments for both populations. This proposal will provide needed insight into the consequences of early tranexamic acid intervention in these significantly injured patients when these impediments exist.

H. Research Design and Methods

H.1. Study Design/Setting: The study will be a 3 year, multi-center, blinded, randomized trial utilizing level-1 trauma centers with busy emergency medical transport services with a clinical research track record. For patients at risk of hemorrhage being transported by emergency medical transport, the infusion of 1 gram of tranexamic acid over approximately 10 minutes in the prehospital setting will be compared to placebo. The University of Pittsburgh Medical Center (UPMC) will be both the clinical outcome and data coordinating center. Each individual institution will perform point of care rapid TEG analysis and coagulation measurements on site. UPMC presbyterian is the busiest level-1 trauma center in the state of Pennsylvania and is affiliated with the largest non-profit air medical service in the country with an extensive track record of multi-center, in-

hospital and prehospital clinical trials. All enrolling centers and respective investigators similarly have busy emergency medical services and significant experience with multi-center trials, the research infrastructure to allow them to successfully occur and have no other clinical investigations that would preclude participation in the current proposal. ***Participating Institutions include: University of Pittsburgh, University of Arizona, University of Texas at San Antonio, and the University of Utah. The University of Tennessee at Memphis will be utilized as an alternate/additional site if required.***

H.2. Study Population: The study population will include blunt or penetrating injured patients at risk of hemorrhage being transported via emergency medical services from the scene of injury or from referring hospital to a definitive trauma center that is participating in the trial. We have selected similar inclusion criteria as the prior large, prospective study[41] (CRASH-2). This represents a similar level of acuity than the CRASH-2 study and additionally allows the mechanism of tranexamic acid's benefit to be characterized across a spectrum of injury severity since the pre-specified analysis of the CRASH-2 trial demonstrated that the mortality benefit attributable to early tranexamic acid remained consistent across patients with low thru high predicted mortality, suggesting its use should not be limited to the most severely injured.[44] The study group may also contain traumatic brain injured patients who represent a subgroup that may also benefit from early tranexamic intervention. [45] Based upon our own current data (2011-2012) in injured patients that require air medical transport, these inclusion criteria are associated with over a 65% blood transfusion rate in the first 24 hours from admission and represents the most pertinent population for the trial.

H.2.1. Specific Inclusion Criteria:

1. Blunt or penetrating injured patients at risk of hemorrhage being transported via emergency medical services from the scene of injury or from referring hospital to a definitive trauma center that is participating in the trial

AND

2. Within 2 hours of estimated time of injury

AND

3A. Hypotension (Systolic Blood Pressure (SBP) < 90mmHg)

i. At scene of injury or during emergency medical transport

ii. Documented at referring hospital prior to emergency medical transport arrival

OR

3B. Tachycardia (heart rate >110 beats per minute)

i. At scene of injury or during emergency medical transport

ii. Documented at referring hospital prior to emergency medical transport arrival

H.2.2 Specific Exclusion Criteria:

1. Age > 90 or < 18 years of age; **2.** Inability to obtain intravenous or intraosseous access;**3**. Documented (radiographic evidence) cervical cord injury with motor deficit; **4.** Known prisoner; **5.** Known pregnancy**; 6.** Traumatic arrest with > 5 minutes CPR without return of vital signs; **7.** Penetrating cranial injury **8**. Traumatic brain injury with brain matter exposed; **9.** Isolated drowning or hanging victims **10.** Wearing an opt out bracelet. **11.** Objection to study voiced by subject or family member at the scene. **12.** Isolated fall from standing

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 emergency medical crew to either directly witness or obtain documentation of inclusion criteria, including qualifying vitals, due to the nature of the emergency pre-hospital setting, there may be occasions where the emergency medical crew must rely on verbal report of qualifying vitals from the referring hospital or ground crew. In these instances, if, after subsequent review of outside hospital and/or ground crew 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 intention-to-treat principle.

In the event that a verbal report must be used in lieu of physical documentation or directly witnessing the qualifying vitals, documentation of the verbal report will serve as the source documentation for determining eligibility. Verbal reports will be documented in the emergency medical record and will detail the information reported and by whom.

H.3. Interventional Arm: The Intervention will have both a prehospital phase and in-hospital phase. Investigational Drug Services (IDS) at the University of Pittsburgh will be utilized to supply and organize both tranexamic acid and placebo along with respective normal saline bolus and infusion bags to all participating trial sites. IDS at the University of Pittsburgh has a long track record of managing large multicenter trials and is currently executing and responsible for over 150 inpatient and outpatient clinical trials.

H.3.1. ***Prehospital Phase Intervention***: Once inclusion and exclusion are verified while the patient is being transported via emergency medical transport to a STAAMP trial participating center, in a randomized, double blinded fashion, either 1 gram bolus of tranexamic acid diluted in 100cc of normal saline (pre-prepared on emergency vehicle) or placebo of identical volume will be infused intravenously or intraosseously (if IO access was obtained due to a clinical need per standard of care) into the patient over approximately 10 minutes ("Bag A"). After receiving the prehospital phase intervention, standard operating procedures utilizing goal directed crystalloid infusion will be followed (see **H.7. Prehospital Standard Operating Procedures** below**)**

H.3.2. ***In-hospital Phase Intervention*****:** Upon arrival, patient blood and labs will be sampled and arrival rapid-TEG analysis will be performed within first 6 hours. After inclusion and exclusion criteria verification by research staff, in a double blinded, randomized fashion, those patients who received tranexamic acid in the prehospital phase will receive 1 of 3 different dosage regimens:

1. *Standard Tranexamic acid Dosing*: 1 gram infusion over approximately 8 hours
2. *Repeat Tranexamic acid Dosing*: 1 gram bolus ***and*** 1 gram infusion over approximately 8 hours
3. *Abbreviated Tranexamic acid Dosing*: No further tranexamic acid to be given

For intervention blinding purposes, each patient will receive both a bolus dose (either tranexamic acid or placebo), "Bag B," and 8 hour infusion (either tranexamic acid or placebo), "Bag C," depending on the randomized dosing regimen. (Figure 13. below)

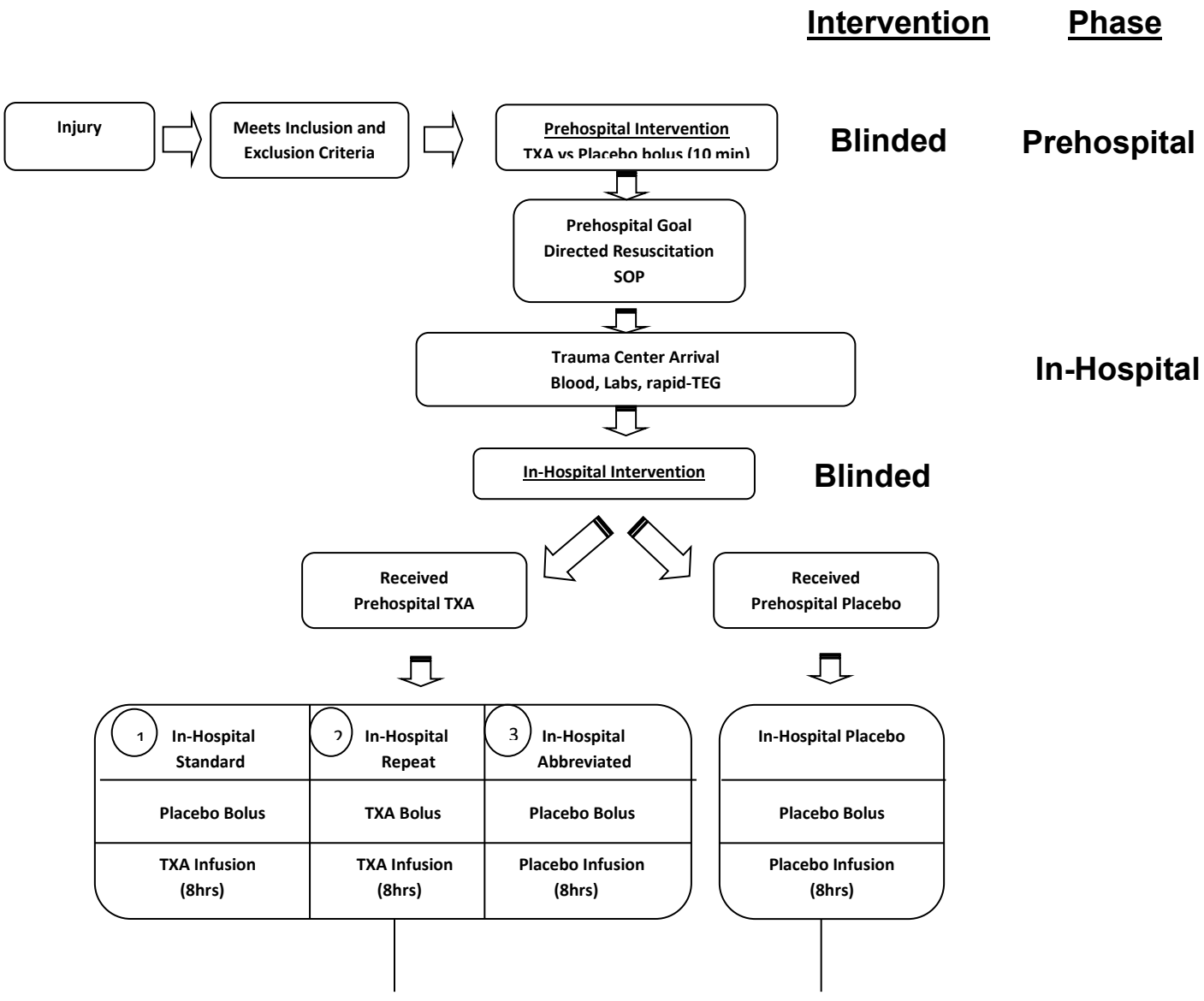
H.3.2.1 ***Adjustment For Renal Insufficiency:*** Subjects with a known or suspected history of renal insufficiency will receive a renal dose adjustment for the 8 hour repeat infusion (Bag C). The Estimated Body Weight Table will be used to determine the dose (Figure 12). The dose will be capped at 1000 mg.

1. *Standard Dosing*: bolus- no dose adjustment / infusion- 1.25 mg/kg/hr x 8hrs
2. *Repeat Dosing*: bolus- no dose adjustment / infusion- 1.25 mg/kg/hr x 8hrs
3. *Abbreviated Dosing*: bolus- no dose adjustment / infusion- 1.25 mg/kg/hr x 8hrs

Renal adjustment will be based upon the most current tranexamic acid Product Information/Package Insert (Cyklokarpon package insert. West Ryde NSW: Pfizer Inc. 2010 October) where renal dosing adjustment is recommended for cardiac bypass surgery patients, whose eGFRis below 29 (< 29 mL/min/1.73m^2).

Estimated Body Weight	Dose
>100 kg	1000 mg (10 ml from vial)
90-99.9 kg	900 mg (9 ml from vial)
80-89.9 kg	800 mg (8 m1 from vial)
70-79.9 kg	700 mg (7 ml from vial)
60-69.9 kg	600 mg (6 ml from vial)
50-59.9 kg	500 mg (5 ml from vial)
40-49.9 kg	400 mg (4 ml from vial)
30-39.9 kg	300 mg (3 ml from vial)
20-29.9 kg	200 mg (2 ml from vial)

Figure 12. Dose adjustment



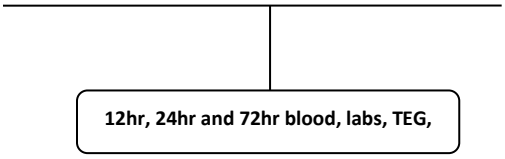


Figure 13. 2-phase Intervention Schematic.

H.4. Placebo/Control Arm: Prehospital phase patients randomized to placebo will receive identical placebo diluted in 100cc of normal saline and infused over approximately 10 minutes. Patients who received prehospital phase placebo will receive in-hospital identical placebo bolus and approximately 8 hour placebo infusion for blinding purposes.

H.5. Randomization: The randomization scheme will have both a prehospital phase and in-hospital phase.

H.5.1. ***Prehospital Phase Randomization***: Individual patients meeting criteria while en route via emergency medical transport will be randomized using an allocation sequence block size of 8 to either 1 gram of tranexamic acid or placebo diluted in 100cc of normal saline given over approximately 10 minutes. A single prehospital treatment box containing ascending numerically labeled (1-8) treatment packs (randomized with a computer random number generator) will be distributed to each respective helicopter base (or station in the case of ground ambulance). In an ascending numerical order fashion treatment packs will be utilized for enrolled patients. The box and treatment pack # will be recorded by research staff upon arrival for all randomized patients. The patient and all treatment and research staff will be blinded to the treatment arm. All intervention vials will be covered to obscure view of vial contents to prehospital staff giving the intervention and amber colored syringes will be utilized to maintain blinding. IDS at the University of Pittsburgh will be unblinded to the prehospital intervention. Additionally, the pharmacy at each respective participating center will have access to the prehospital randomization/assignment scheme once the prehospital intervention box and treatment # are provided to them by the accepting research staff at each participating center.

H.5.2. ***In-hospital Phase Allocation*****:** Using a web based, randomization assignment program built specifically for the trial, research staff will provide and input the prehospital intervention box # and treatment pack # into the web based platform at each site and be provided the In-hospital treatment allocation to be utilized for the second phase intervention. IDS at the University of Pittsburgh and each respective pharmacy at the participating sites will be provided with the random allocation sequence and will be unblinded to the in-hospital allocation assignment. The accepting research staff and pharmacy will verify they have the same in-hospital phase treatment assignment as an additional check to the allocation assignment. An allocation sequence based upon a block size of 9 again generated with a computer random number generator will be utilized for those who received prehospital Tranexamic Acid. Each respective IDS or pharmacy will prepare the inhospital phase treatment (approximate 10 minute and 8 hour infusion). The patient and all treatment and research staff will be blinded to the treatment that is received.

H.6. Blinding: The trial is a double blinded trial for both the prehospital phase and in-hospital phase interventions. The participants, investigators, research coordinators and staff, and persons having any contact with the patients will be blinded to study treatment assignments. The IDS at the University of Pittsburgh will be unblinded to the prehospital phase treatment arm and the respective pharmacy at each center will be unblinded once the treatment prehospital treatment information is provided to them by research staff. Both IDS at the University of Pittsburgh and the respective IDS or pharmacy at each center will be unblinded to the in hospital treatment assignment.

H.7. Prehospital Standard Operating Procedures: To minimize over exuberant crystalloid resuscitation during the prehospital phase of treatment after enrollment, further crystalloid resuscitation post-intervention will follow a 'goal directed' standard operating procedure (SOP). Crystalloid infusion following the intervention will be based upon hemodynamic status (SBP < 90mmHg) with infusion of 500cc boluses of crystalloid for those patients with persistent hypotension. Normotensive patients will receive crystalloid infusion at maintenance rate. (Figure 13. above) All crystalloid volumes will be monitored relative to transport time for all

patients and across enrolling sites. To minimize important differences for the early pre-hospital management of each patient, scene time, referral hospital time and definitive transport times for emergency medical services will be obtained, recorded and monitored including pre-hospital interventions.

H.8. In-hospital Standard Operating Procedures: We have selected level I, academic, trauma centers with busy emergency medical transport services that are recognized for providing high level care of the injured patient. As the intervention begins in the pre-hospital setting, there exists the potential for in-hospital management differences to occur across centers as in any multi-center study which does increase the study results applicability. However, to minimize those differences where high level evidence exists for the early in-hospital management of each patient, and throughout a patients' admission, SOPs for resuscitation and transfusion will be employed over the initial 24 hours and throughout a patients' admission. SOPs for patients who are at risk of massive transfusion will target an FFP:PRBC ratio of at least 1:2 based upon currently available data. Once 48 hours has passed without ongoing blood transfusion requirements, standard transfusion practice evidence in the ICU will be followed including standard restrictive transfusion guidelines for each respective institution in line with the TRICC trial recommendations (transfusion trigger of hgb- 7.0).[89]

I. Outcome Variables/Definitions

I.1. Primary Outcome: The primary outcome which will be utilized to power the study will be 30 day mortality. We anticipate that this study will be conducted with an exception from consent for emergency research and will require FDA approval. We will power the study using 30-day mortality as the primary outcome variable.

I.2 Secondary Clinical Outcomes: Secondary clinical outcomes will include the incidence of hyperfibrinolysis (EPL > 7.5% by rapid-TEG analysis) upon arrival to the trauma bay within the first 6 hours, the incidence of acute traumatic coagulopathy (INR > 1.4), 24 hour mortality, acute lung injury, multiple organ failure, the development of nosocomial infection, early (24hr) seizures, in-hospital pulmonary embolism, presenting base deficit, 24 hour crystalloid requirements and 6 hour and 24 hour blood and blood component transfusion requirements (PRBC, FFP and platelets). ***These same clinical outcomes will similarly be used for the randomized tranexamic acid dosage regimen comparison.***

I.3. Secondary Laboratory/Mechanistic Outcomes: All laboratory/mechanistic outcomes will be measured during the first 6 hours from trauma center arrival and at 12 and 24 hours (+/- 12 hours) out from injury. Those laboratory/mechanistic outcomes including flow cytometry which require fresh blood samples will be performed only at the University of Pittsburgh on a subset of patient samples unless participating centers have specific capabilities and following appropriate training for standardization. ***These same laboratory/mechanistic outcomes will similarly be used for the randomized tranexamic acid dosage regimen comparison at 12 and 24 hours post-injury.***

I.4. Clinical Outcomes Methods/Definitions: All clinical outcomes will be prospectively evaluated for throughout ICU and hospital admission and the timing from the day of initial injury will be recorded for time-to-event statistical analysis.

I.4.1. 30 day and 24 hour mortality: 30 day mortality will be prospectively recorded from the day of trauma bay arrival. Over the first 24 hours we will document and record the time of death in hours. We suspect that patients enrolled will have a significant percentage of mortality that occurs in the first 24hrs.

I.4.2. Acute lung injury: Development of acute lung injury will be assessed utilizing the 1992 American-European Consensus Conference definition[90] which includes: 1) bilateral infiltrates on cxray, 2) a capillary wedge pressure < 18mmHg, and 3) Pao2/Fio2 ratio < 300 via blood gas analysis. In those patients without a Swan-Ganz catheter (vast majority) to determine capillary wedge pressure, the absence of signs of or clinical concern for elevated left sided atrial pressures will be used for the diagnosis. All patients who remain intubated beyond the first 24 hours post injury will be evaluated using blood gas analysis and cxray evaluation. Those patients who remain intubated at 48 hours thru 7 days will be reevaluated for this outcome at these time points. All time variables to the respective

outcome event will be determined from the day of initial injury for time-to-event analysis and multivariate Cox proportional hazard regression analysis.

I.4.3. Nosocomial infection: Infectious outcomes of interest will include ventilator associated pneumonia, blood stream infection and urinary tract infections. Surgical site infections and post-operative intra-abdominal collections will also be recorded but excluded as a principal secondary outcome event to reduce the confounding effects of operative interventions which not all patients require. The development of these nosocomial infections will be based upon positive culture evidence during hospital admission. Infections will be monitored until post injury day 30 or ICU discharge. Diagnosis of ventilator associated pneumonia requires a quantitative culture threshold of $\geq 10^4$ CFU/ml from broncho-alveolar lavage specimens in addition to standard x-ray and clinical criteria. Diagnosis of catheter-related blood stream infections requires positive peripheral cultures with an identical organism obtained from either a positive semi-quantitative culture (>15 CFU/segment), or positive quantitative culture ($>10^3$ CFU/segment) from a catheter segment specimen. Urinary tract infections required $> 10^5$ organisms/ml of urine. All time variables to the respective outcome event will be determined from the day of initial injury, while the time to the first nosocomial infection will be used in those patients with multiple infections for time-to-event analysis and multivariate Cox proportional hazard regression analysis.

I.4.4. Multiple organ failure: Organ dysfunction will be evaluated via a well-validated scoring system referred to as the Denver Postinjury Multiple Organ Failure Score.[91-93] Patients who are never admitted to the ICU or those with a length of ICU stay of less than 48 hrs will be considered to have a Denver score of 0. A summary of the Denver score may be calculated by summing the worst scores of each of the individual systems over the course of the ICU stay. A summary Denver score > 3 will be classified as multiple organ failure (MOF). Scores will be determined daily up until post injury day 30 or ICU discharge. All time variables to the respective outcome event will be determined from the day of initial injury, for time-to-event analysis and multivariate Cox proportional hazard regression analysis.

I.4.5. Early seizures: Seizures will be prospectively monitored for over the first 24 hours from injury. Whether the seizures occurred post-operatively or in those patients who did not require operative intervention will be documented. Neurology consultation will be sought in those patients with seizure activity. Classification of seizure type and management will be based upon formal neurology consultation. Repeat occurrence and outcomes associated with seizure will similarly be documented.

I.4.6. In-hospital pulmonary embolism: Pulmonary embolism 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.

I.4.7. **Blood and blood component transfusion and resuscitation requirements**: 6 and 24-hour transfusion requirements for blood, fresh frozen plasma and platelet transfusion will be determined by recording the number of units transfused for each component from the time of trauma bay arrival. Transfusion components which are initiated will be considered transfused irrespective of completion. Similar determinations for crystalloid requirements (volume in cc's) over the first 24hrs of injury will occur.

I.4.8. Adverse Events: An adverse event (AE) is defined as any untoward medical occurrence in a trial subject undergoing a study procedure or administration of a study drug. Thus, an AE is an unfavorable sign, symptom, or disease temporally associated with the study intervention, irrespective of whether it is considered related to the study intervention. A reportable AE is defined as an unexpected, serious event related or possibly related to the study intervention or procedures.

I.4.9. Unexpected Adverse Events: Unexpected adverse events will be defined as any serious unexpected adverse effect on health or safety or any unexpected life-threatening problem caused by, or associated with the interventions if that effect or problem was not previously identified in nature, severity, or degree of incidence in the investigation plan or application (including a supplementary plan or application), or any other unexpected serious problem that relates to the rights, safety or welfare of subjects.

I.4.10. Expected Adverse Events: Expected adverse events are commonly observed in patients who are at risk of hemorrhage following traumatic injury and may or may not be attributable to the tranexamic acid intervention. These will be monitored and reported throughout the time period for the trial. Clinical diagnoses of pneumonia, sepsis, cerebral bleeding, stroke, seizures, surgical interventions, complications due to specific injuries as well as other major medical or surgical complications are commonly observed in these patients. They will be recorded as noted in the hospital discharge summary.

I.5. Laboratory/Mechanistic Outcome Methods/Definitions: All measurements will be performed within 6 hours of arrival and at 12 and 24 hours post injury (+/- 12 hours) for the randomized dosage regimen comparison. One more additional blood sample will be collected at 72 hours (± 12 hrs) for D-dimer, activated Protein C levels and plasmin-antiplasmin complexes measurements.Excluding r-TEG analysis and PT/ INR measurements, all blood and serum samples will be spun, stored and batched at their respective institution and delivered to the University of Pittsburgh where formal ELISA immunoassay measurements will be undertaken**.** Those laboratory/mechanistic outcomes including flow cytometry which require fresh blood samples will be performed only at the University of Pittsburgh on a subset of patient samples unless participating centers have specific capabilities and following appropriate training for standardization.

I.5.1. Coagulopathy and TEG parameters (Aim#2): To appropriately characterize differences in coagulopathy between tranexamic acid and placebo, in addition to r-TEG measurements of hyperfibrinolysis, presenting PT/ INR and additional TEG parameters will also be measured (ACT, r-value, k-time, α-angle, maximal amplitude, and G-values). All rapid TEG measurements will be performed within 6 hours of arrival and at 12 and 24 (+/- 12 hours) hours post injury. TEG analysis will be performed on a TEG® 5000 Thromboelastograph® Hemostasis Analyzer which will reside within the emergency department of each participating site**.** Standard laboratory INR will be drawn and measured at each institution within 6 hours of arrival and at 12 and 24 hours (+/- 12 hours). To further quantify the coagulopathy and hyperfibrinolysis post injury in these patients, D-dimer, activated Protein C levels and plasmin-antiplasmin complexes will be measured by ELISA plate assay. (ANIARA, USCN Life Science Inc., DRG International, Inc.) Plasmin-antiplasmin complexes may represent a more common, subclinical measurement of fibrinolytic activity that is not able to be assessed using standard TEG analysis, but elevated levels are associated with significantly worse outcome post injury and may be a marker than demonstrates the mechanism by which tranexamic acids has it beneficial effects.

I.5.2. Exploratory Inflammatory Response Outcomes (Aim#3): Plasmin has pro-inflammatory effects by activating monocytes, neutrophils, platelets, endothelial and dendritic cells and induces pro-inflammatory genes.[51,52] Plasmin also induces chemotaxis of monocytes and dendritic cells and in-vitro and in-vivo studies have demonstrated the ability of plasmin to stimulate the production reactive oxygen species and promote the release of lipid mediators and cytokines via complement activation.[51,53] To appropriately characterize the potential non-antifibrinolytic mechanisms responsible for the mortality benefit attributable to tranexamic acid, serum plasmin levels, and plasmin mediated compliment activation (C3a and Factor B) and HMGB1 levels will be measured by ELISA plate assay for all enrolled patients (MyBioSource, BD Biosciences). A Cytokine 10-plex Panel for the Luminex® platform will be utilized for all early inflammatory cytokine measurements. (Novex®) These same inflammatory response measurements will be utilized for the randomized dose regimen comparison at 12 and 24 hours post injury.

I.5.3. Platelet, Leukocyte and Inflammatory Gene Expression Measurements (Aim#3): To further characterize an anti-inflammatory effect of tranexamic acid mediated thru reduced plasmin activation, for those patients enrolled at the University of Pittsburgh, whole fresh blood will be obtained and platelet and leukocyte activation will be measured on a subset of patient samples using flow cytometry (FACS) analysis utilizing platelet activation specific antibodies (CD41 and CD62P, Molecular Probes®) and Leukocyte activation specific antibodies (CD11a and CD35, Molecular Probes®). Inflammatory gene expression will be assessed via RT-PCR with a focus on evidence based gene targets including those identified as being most dramatically perturbed following severe injury from the *Glue Grant* study cohort including CD177, MMP8, lactotransferrin, haptoglobin, S100A8 (calgranulin), MYBL1

(myeloblastosis viral homologue, v-myb*),* KLRF1 (Killer cell lectin like receptor subfamily F, member 1), TGFBR3 (TGF-β receptor III subunit*),* and TCRA (T cell receptor α subunit).[94] These studies will be performed at a University of Pittsburgh FACS and RT-PCR core facilities which will be available 24 hours/day over the three years of the study.

J. Analysis Plan:

The overarching goal of the study proposal is to assess the efficacy of prehospital tranexamic acid as compared to placebo for injured patients at risk for traumatic hemorrhage who require emergency medical transport. Additional goals include dose regimen comparison and characterization of the mechanisms responsible for tranexamic acid's beneficial effects. All primary and secondary analyses will be performed based on the Intent-to-Treat principle for the prehospital randomization and analyses will include all enrolled patients grouped by randomization assignment.

J.1. Data Analysis for Primary Outcome: We follow an intent-to-treat approach in analyzing our primary outcome of 30 day mortality.

J.1.1. Primary Primary Outcome (30 Day Mortality): All randomized subjects will be included in the analysis to test the differences in 30 day mortality. 30 day mortality will be computed at the end of study and stated as a dichotomous variable. For subjects who have not been reported as deceased by day 30 following admission from any of the sources queried we will use multiple imputation under the assumption that the missing data are not missing at random. The process for determining whether or not a subject is deceased at 30 days is described in detail in section (**N.6.)**. If more than 15% of the subjects are missing the 30 day outcome, we will consider this outcome as descriptive only. We will analyze this endpoint as a fixed point in time using a two-sided Mantel-Haenszel (M-H) test taking site, the stratifying variable (strata), into account. The M-H test is robust to lack of homogeneity of odds ratio although power would be reduced. This approach has more power than the survival analysis described below given the potential for crossing hazard functions. We will also test homogeneity of the odds ratios across sites using the Breslow-Day test. We will compute 95% confidence intervals on mortality by treatment group at 30 days. We will also conduct a sensitivity analysis of 30 day mortality to assess the effect of imputation 'as alive' on the treatment group comparisons and confidence limits for the 30 day outcome. To provide further insight we will compute 30-day survival curves. Survival time will be compared between treatment arms using Cox proportional hazards model with site as a covariate. If the proportional hazards assumption is violated we will include a time treatment interaction in the model and choose the appropriate approach. As an additional analysis, we will use the same Cox proportional hazards approach to adjust for baseline covariates such as demographics, injury severity, presenting vital signs, and prehospital time. Since site is a stratifying variable it will be included as a random effect. We will do pre-screening of covariates other than site at the 0.20 level before fitting the final model if our sample size is not sufficient to include all covariates in the model. We would follow the approach above to test for and take crossing hazards into account if applicable. As an additional exploratory analysis we will compare 30-day survival in the two groups adjusting for the covariates listed above and any additional baseline covariates that are imbalanced between treatment groups ($p<0.10$) using the same screening approach to decrease the number of covariates included in the model, if necessary.

J.2. Analysis of Prehospital Randomized Secondary Outcomes: Unless there is sufficient power (predetermined before the analysis is begun), the approach to analysis of secondary endpoints will generally be calculation of confidence limits on intervention group differences or model parameters rather than formal tests of significance at a specified critical level as the trial will not have sufficient power to detect difference in all of these outcomes. However, these comparisons will add to the knowledge of the benefits and risks of the interventions. Parametric and nonparametric comparisons will be applied according to normalcy. All tests used will be two-tailed tests at significance level (alpha) of 0.05. *For prehospital randomized clinical outcomes* we will use Chi-square with 95% confidence intervals for dichotomous outcomes and parametric or non-parametric testing for continuous variable with 95% confidence intervals. *For prehospital randomized laboratory or exploratory outcomes* we will use parametric or non-parametric testing for continuous variable with 95% confidence intervals.

J.3. Analysis for Second Stage In-hospital Randomized Dosage Regimens: Chi-square test will be able to test the effect of different tranexamic dosage regimens on hyperfibrinolysis. Similarly, chi-square will be used to detect any differences between dosage groups for 30 day mortality. To detect a trend in dosage response, test for trend will be implemented. As additional analysis and to account for site and to adjust for some important covariates, we will use logistic regression to test the effect of dosage on hyperfibrinolysis. Similarly Cox proportional hazards regression can be used for 30 day mortality. *For In-hospital randomized dosage regimen comparison for clinical outcomes* we will use Chi-square with 95% confidence intervals for dichotomous outcomes and parametric or non-parametric testing for continuous variable with 95% confidence intervals. *For In-hospital randomized dosage regimen comparison for laboratory or exploratory outcomes* we will use parametric or non-parametric testing for continuous variable with 95% confidence intervals.

J.4. Predefined Subgroup Analyses: Predefined subset analyses will be performed looking at 1.) patients who ultimately did or did not required blood transfusion 2.) those patients with significant traumatic brain injury (Head AIS >2) versus those without significant brain injury (Head AIS ≤ 2), 3.) those patients enrolled from the scene of injury versus those enrolled from a referral hospital, 4.) those patients that require operative intervention in the first 24 hours, 5.) those patients with a preinjury history of vitamin K antagonist medication history versus those without, 6.) those patients with preinjury history of antiplatelet medication history. 7.) those patients who ultimately did or did not require massive transfusion (≥ 10 units blood in first 24hrs). 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.

J.5. Randomization of Ineligible Subjects: It is anticipated that there will be a small proportion of patients enrolled who receive either tranexamic acid or placebo that in retrospect will not have met the entry criteria and are thus ineligible. In this circumstance, patients will be analyzed according to the group to which they were randomized. Subgroup analyses based on eligibility criteria will be performed if the number of patients so affected is large. However, based on the relatively limited inclusion and exclusion criteria it is anticipated that the frequency of this event will be low.

J.6. Non-adherence: In some circumstances, patients may receive the incorrect treatment packet. Non-adherence is most likely to occur in the case of the exsanguinating patient when time is limited and the wrong treatment pack is utilized. Fortunately, this event is relatively rare. In keeping with the intention-to-treat analytic design, these patients will be analyzed with the group to which they were to be randomized to.

J.7. Missing Data: For 30-day mortality, given the transient nature of many of the subjects, extensive efforts will be made to ascertain vital status (**see N.6**.). Batch searches of the mortality databases will continue every quarter for subjects with unknown status, until trial closeout. For interim and final analyses, subjects who have not been reported as deceased by day 30 following ED admission from any of these sources we will use multiple imputation for the final value. As sensitivity analyses we will report the data with and without imputation. We will also report an analysis consistent with that used in other studies counting those missing as alive on day 30.

K. Sample Size Justification and Power Analysis:

We have determined the sample size for this proposal and powered the analysis based upon the primary outcome, 30 day mortality.

K.1. Primary Outcome 30 day mortality: Assuming a baseline mortality risk of 16% as was demonstrated in the Crash-2 study[41,43] with 30 day mortality as the primary outcome, using a two-sided Z test with pooled variance and a 2 sided alpha of 0.05 the study will have a 90% power to detect a 7% or greater difference in 30

day mortality. The study will have 80% power to detect a 6% or greater difference in 30 day mortality. Using this power analysis, **497 patients in each arm, 994 total patients will be required, with a power of 0.85 and 2 sided alpha of 0.05. This will require on average each center to enroll 80 patients per year or 1 to 2 per week.** As busy, level 1 trauma centers with robust emergency medical programs were screened using the proposed inclusion criteria over 2012 data and selected for participation based upon this information, this sample size estimate is appropriate and attainable.

Power	Sample Size Grp 1 N1	Sample Size Grp 2 N2	Prop|H1 Grp 1 or Trtmnt P1	Prop Grp 2 or Control P2	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actual Alpha	Beta
0.9000	497	497	0.0919	0.1600	0.0000	-0.0681	0.0500		0.1000
0.8500	497	497	0.0965	0.1600	0.0000	-0.0635	0.0500		0.1500
0.8000	497	497	0.1003	0.1600	0.0000	-0.0597	0.0500		0.2000

L. Human Subjects:

We anticipate that this study would be conducted with an exception from 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.

Community consultation as outlined by the local IRB will be undertaken prior to IRB approval. Since the population eligible for enrollment includes all citizens in the study regions it will not be possible to target any particular small group. Feedback from the community will be obtained by research personnel regarding any concerns they may have about potential enrollment. If requested, bracelets will be made available that could be worn by members of the community who do not want to participate. Public notification and community consultation will be performed as directed by the local IRB and may include such methods as using random digit dialing telephone surveys of the proposed study community, targeted small group meetings or consultation with community leaders. Due to ongoing participation in large multicenter research organizations, our institution and participating centers have significant experience with community consultation and notification practices.

Benefits of participation in the STAAMP trial for both interventional and control subjects:

A unique benefit regarding participation in the STAAMP trial is that all research results for both Tranexamic acid and control arms of the study may be used to further inform clinical care decisions throughout a participants hospital stay. Participation in the trial may also aid in early recognition of trauma induced coagulopathy due to the early measurements of INR and thrombelastography (TEG) which will be performed on all enrolled subjects. TEG is an FDA approved tool, however, currently it is not standard of care and only a small proportion of trauma centers across the country routinely obtain early INR and point of care rapid-TEG analysis in the emergency department, soon after arrival in patients in hemorrhagic shock. Early recognition of coagulopathy for all enrolled subjects may lead to earlier intervention and in hospital mechanisms that improve clinical outcome.

M. Screening, Enrollment and Notification:

The Department of Surgery at the University of Pittsburgh has interdepartmental research affiliations with the Department of Critical Care Medicine and the Department of Emergency Medicine and has spearheaded the Multidisciplinary Acute Care Clinical Research Organization (MACRO). MACRO is a unique,

interdepartmental resource with laboratory facilities, an experienced and professionally-trained staff of clinical research coordinators, and 24 hour around the clock screening capabilities. They have extensive experience with data entry, multi-center data coordination, training, IRB liaison needs, web-based data entry platforms and specimen management and storage. MACRO follows a cost center model and provides 'cost-neutral' services to clinical investigators from diverse specialties in order to conduct clinical and translational research. The University of Pittsburgh will be the data and specimen coordinating center for the proposal. MACRO research coordinators and participating site research coordinators will document and verify all trauma arrivals via emergency medical transport for enrollment. Those patients who met inclusion and exclusion criteria en route via emergency medical transport that were enrolled will be verified and enrolled patients will undergo initial laboratory and blood sampling and will have point of care rapid thromboelastography (TEG) performed for coagulation parameter measurements within 6 hours of patient arrival. **All guidelines and requirements for notification for exception of consent for emergency research will be followed.** Patients at risk for hemorrhage during or directly preceding emergency medical transport represents an immediate life threatening condition with the patient commonly intubated, unconscious, or not responsive, it will not be possible to contact legal representatives at the time of study entry. Research coordinators will make every effort to contact legal representatives after admission to the hospital to notify them that the patient was enrolled in a randomized trial. Research personnel will attempt to contact the subject's legally authorized representative as soon as feasible for notification of enrollment and will provide an opportunity to opt out from ongoing participation. Summary of these efforts will be documented in the patient's chart. If the subject becomes competent during the study period then he/she will be approached by research personnel for notification of enrollment and a similar provision of an opportunity to opt out from ongoing participation.

We will inform the family member or LAR at the earliest feasible opportunity of the subject's inclusion in the clinical trial, the details of the trial, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The therapeutic window for this trial is zero due to prehospital nature of this trial. Such notification is not usually feasible before or at the actual time of treatment or trial enrollment and must be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by a local IRB). A log will be kept to document the attempts made to contact the LAR/family member. The log will be included in the paper data collection forms.

The investigators will utilize social workers and law enforcement personnel to try to locate the patient's legally authorized representative. If that search is unsuccessful, a notification letter will be sent to the subject's authorized representative explaining the study and providing contact information for answering questions. The letter will be sent via registered mail or by UPS and documentation of the addressee and date of mailing will be kept.

N. Data

N.1. 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.
N.2. Prehospital Resuscitation Elements: Demographics, emergency medical response times (call receipt to arrival, arrival at patient side,) injury characteristics, vital signs, prehospital resuscitation characteristics, (plasma volume, crystalloid volume, blood transfusion volume, starting at referring hospital or scene) prehospital interventions (needle decompression, chest tubes) referring hospital vitals, and interventions.
N.3. In-Hospital Resuscitation Elements: Demographics, shock severity (base deficit, lactate), injury characteristics, ED vitals, ED interventions (chest tubes, intubation), operative interventions and timing of interventions, injury severity score, ICU days, ventilator days, length of stay, multiple organ dysfunction scores (daily), nosocomial infectious outcomes, blood gas results, cxray reads, transfusion of blood and blood components, resuscitation requirements, all primary and secondary outcomes.

N.4. Data Entry: MACRO and associated internet technology affiliates at the University of Pittsburgh will create web-based data entry platform to collect necessary information from all participating sites which will also be utilized for randomization assignment. Web entry forms will have dynamic features such as immediate checks on data and relationships within a form and between forms. Details and clarification about data items will be provided using pop-up windows and links to appropriate sections of the on-line version of the Manual of Operations. Data encryption and authentication methods will be used. Additional features will be built into the web entry forms including: forms transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms.

N.5. 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 periodically (e.g. weekly) to a data repository that can be used by statistical software packages. These data sets 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. Backup of data and programs will be performed at frequent intervals. Access to data will be limited to those who need access to perform their tasks. The database management system is able to manage large quantities of data, to merge data from multiple databases as required, to handle complex and possibly changing relationships, and to produce analysis datasets that can be imported into a variety of statistical packages.

N.6. Mortality Outcome Data (30 day): If discharge occurs before hospital day 30 and the subject is discharged to a hospice, nursing home or other healthcare provider, research staff will contact the facility to ascertain the subject's vital status. If the subject is discharged to his/her usual residence before day 30, the research staff will contact the subject or their family/legally authorized representative (LAR). If vital status remains unknown the clinical site will request periodic searches for the subject's social security number in the Social Security Master Death Index, the respective State Health Department's vital statistics/mortality database, and the mortality databases of a credit reporting agency, e.g., Experian. For subjects not reported as deceased by these sources by day 30 following ED admission, batch searches of the mortality databases will continue every quarter until trial close-out. Date (and cause of death when available) for out-of-hospital deaths will be documented; however, underlying and contributing causes of death may not be available from these sources. Clinical sites will follow local and state HIPPA guidelines for release of PHI for research.

O. Training and Participating Site Coordination:

As the coordinating center for the proposed trial, the University of Pittsburgh will be responsible for all research coordinator training, prehospital provider training, sample and data collection, and maintenance of data integrity. Research coordinators, prehospital 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, prehospital procedures and SOPs, and rapid thromboelastography (TEG) performance. Training verification and retraining will occur at yearly intervals or more commonly if new staff is hired at individual participating sites. 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 via site visit and random patient audit and then annually.

P. Safety Monitoring

P.1. Data Safety Monitoring Board (DSMB): Data safety and monitoring over the course of the clinical trial will fall under the responsibility of an independent data safety and monitoring board. The DSMB will consist of at a minimum, a hematologist with expertise in transfusion medicine, a trauma/critical care surgeon, an epidemiologist with expertise in clinical trial design, and a biostatistician all of whom will have no proprietary interest in the outcome of the trial. The responsibilities of the DSMB will fall under several domains. Prior to beginning the accrual of subjects, the DSMB will review the research protocol and identify logistic problems that may pose problems with randomization schemes and distribution of Tranexamic acid. At this early phase,

the DMSB will also review the plans for data and safety monitoring. At the time of interim analyses, the DMSB will aid in identifying problems surrounding patient accrual and randomization, data collection and follow-up. At this time, the DMSB will also perform an assessment of safety through the comparison of adverse events across both study arms. Lastly, it will fall under the domain of the DMSB to establish whether further conduct of the trial is unnecessary due to strong evidence of benefit or futility.

Although the DSMB will make the final decision about the interim monitoring plan, we anticipate that the DSMB will evaluate the rate of adverse events between the treatment and control arms at 6 months and then annually during enrollment. The DSMB will also monitor primary, secondary study outcomes between the treatment and control groups including main effects and a priori subgroups as specified elsewhere in the protocol. The DSMB will advise the investigators if a change in the protocol is warranted based on this interim monitoring.

P.2. Research Monitor

The Research Monitor is responsible to oversee the safety of the research subjects and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

P.3. Assessing and Reporting Adverse Events (AEs): All Adverse Events will be documented and assessed for relationship to the study intervention. Reporting forms will be submitted to the DSMB and IRB. All potential adverse events will be reviewed as to treatment arm and further classified by: a) Severity (life-threatening, serious, non-serious); and b) Expected vs. Unexpected. For serious adverse events, the coordinating center will notify the DSMB as well as appropriate regulatory agencies, site, and sponsor promptly. The coordinating center will tabulate and report compliance, data quality, and non-serious adverse events on a regular basis. Life-threatening or fatal unexpected AE associated with the study intervention or procedure should be reported within 24 hours of discovery with subsequent follow-up submission of a detailed written report. Serious AEs and unexpected AEs associated with the use of the study intervention or procedure must be reported to the DSMB and IRB within 5 working days with follow up submission of a detailed written report. The DSMB will determine if the event merits an immediate review.

A summary report of the DSMB's findings will be submitted to regulatory agencies. At least one specialized clinician from the Data Safety Monitoring committee will be responsible for monitoring data safety. All related unanticipated problems will be directly handled by study's PIs and reported accordingly. We will also follow Department Of Defense Unique requirements documentation. The University of Pittsburgh and each participating center will have an AE logbook to record and to assure adequate attention for continuous assessment, analysis, and reporting of adverse effects using a standardized report form. The coordinating center will be responsible for all oversight of these risk assessments with monthly evaluations.

P.4. Interim Analyses: In concert with the DSMB, prior to initiation of the trial, the final monitoring plan will be developed to serve as the guide to the DSMB's decision-making process concerning early stopping of the trial. We will recommend interim analyses as 1/3 and 2/3 of patient enrollment. In making the decision to recommend termination of the study, the DSMB shall be guided by several types of information: (i) a formal stopping rule based on the primary analysis (comparison of treatment groups on the in-hospital mortality and 24 hour blood transfusion requirements), (ii) information on safety outcomes by treatment group, (iii) consistency between results for primary and secondary outcomes, and (iv) consistency of treatment effects across subgroups. Formal interim analyses will be performed at 6 months and then annually throughout enrollment . The DSMB will use the results of implementing the stopping rule as a guideline in evaluating the evidence for treatment effects. In making a recommendation to terminate the study, the DSMB will also consider information on safety outcomes, as well as consistency of outcomes for secondary outcomes and consistency of outcomes within important subgroups as described previously. The group sequential method described by O'Brien and

Fleming will be used to develop stopping rules to limit the impact of repeated testing on the probability of a Type I error.[95]

Based on our power analysis, sample sizes of 497 in interventional group and 497 in control group can achieve 80% power to detect a difference of 0.06 between the group proportions of 0.10 and 0.16 at a significance level (alpha) of 0.05 using a two-sided z-test.

We have proposed two interim analyses in this trial. We have based our testing on group sequential design that dividing patient entry into a fixed number of equal-sized groups and provides ethical and practical ways to make decision to stop the trial or continue based on repeated significance tests of the accumulated data after each group is evaluated.

According to the above power calculation and following the group sequential method described by O'Brien and Fleming in developing stopping rules to limit the impact of repeated testing on the probability of a Type I error, we will have equally spaced looks at 33%, 67% and 100% of patient accruals. This is equal to 166, 332, and 497 subjects in each group at these three looks. The following table and graph provide in details information in relation to alpha spending functions to determine the test boundaries according to O'Brien-Fleming method.

Details when Spending = O'Brien-Fleming, N1 = 497, N2 =497, P1 = 0.10, P2 = 0.16

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.33	-3.71030	3.71030	0.000207	0.000207	0.000207	0.018687	0.018687
2	0.67	-2.51142	2.51142	0.012025	0.011890	0.012097	0.399207	0.417894
3	1.00	-1.99302	1.99302	0.046259	0.037903	0.050000	0.382494	0.800388
Drift 2.82089								

Look: These are the sequence numbers of the interim tests.

Time: These are the time points at which the interim tests are conducted. This is also related to proportion of subject accruals

Lower and Upper Boundary: These are the test boundaries. If the computed value of the test statistic *z* is between these values, the trial should continue. Otherwise, the trial can be stopped.

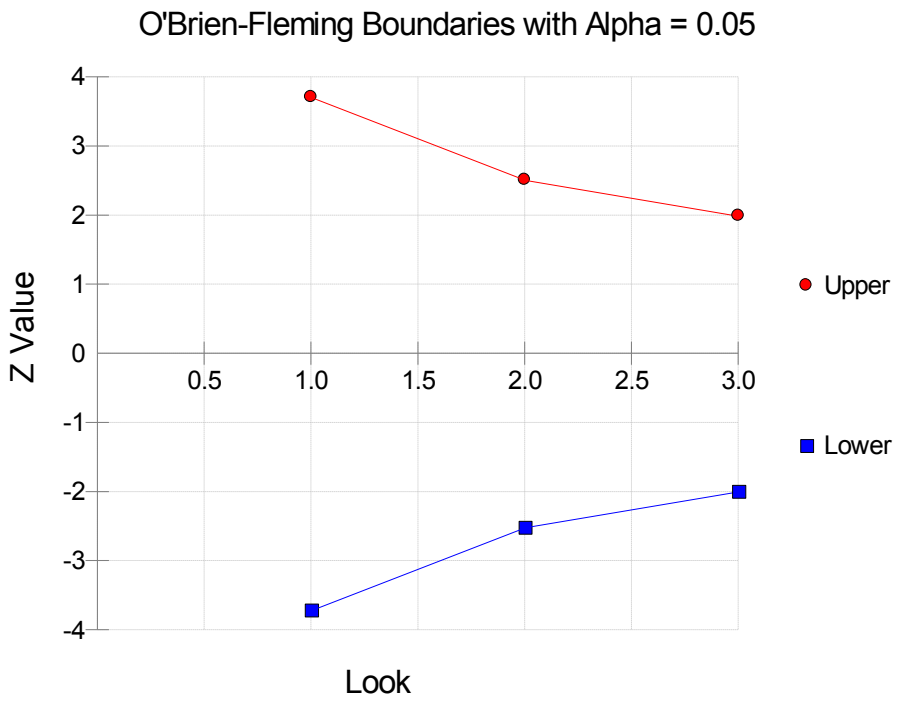
Nominal Alpha: This is the value of alpha for these boundaries if they were used for a single, standalone test. Hence, this is the significance level that must be found for this look in a standard statistical package that does not adjust for multiple looks.

Inc Alpha: This is the amount of alpha that is *spent* by this interim test. It is close to, but not equal to, the value of alpha that would be achieved if only a single test was conducted. The difference is due to the correction that must be made for multiple tests.

Total Alpha: This is the total amount of alpha that is used up to and including the current test.

Inc Power: These are the amounts that are added to the total power at each interim test. They are often called the exit probabilities because they give the probability that significance is found and the trial is stopped, given the alternative hypothesis.

O'Brien-Fleming boundary values are inversely proportional to the square root of information levels on the standardized Z scale (O'Brien and Fleming 1979). The O'Brien-Fleming boundary is conservative in the early stages and tends to stop the trials early only with a small P-value. But the nominal value at the final stage is close to the overall P-value of the design.



The above plot shows the interim boundaries for each look. This plot shows very dramatically that the results must be extremely significant at early looks, but that they are near the single test boundary (1.96 and -1.96) at the last look.

Interim Analysis References

1. Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.
2. Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.
3. O'Brien, P.C. and Fleming, T.R. 1979. 'A multiple testing procedure for clinical trials.' Biometrics, 35, pages 549-556
4. Pocock, S.J. 1977. 'Group sequential methods in the design and analysis of clinical trials.' Biometrika, 64, pages 191-199
5. Reboussin, D.M., DeMets, D.L., Kim, K, and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

P.5 IP Stopping Rules: Study product administration should not be stopped except for in the rare instance that necessary treatment or clinical condition would be contraindicated to TXA administration, patient has a confirmed (as determined by an attending physician) seizure during administration, or if the patient is experiencing a suspected allergic reaction to the study product.

Q. Quality Control and Assurance

Q.1. Protocol Compliance and Reporting: The PI or participating site investigators will not deviate from the protocol for any reason without prior written approval from the IRB except in the event of medical emergency. In that event, the PI will notify the IRB immediately and request approval of protocol deviation. The PI will inform the IRB about all protocol deviations, safety information and other changes. Persistent or serious noncompliance may result in termination of the study. The PI is responsible for reporting all deviations to the University of Pittsburgh IRB and their respective IRB for participating sites. If changes to the design of the study are made by the PI, a protocol amendment must be submitted to the University of Pittsburgh IRB. Changes in the protocol cannot be instituted until appropriate approval has been given by the IRB.

Q.2. Investigator Responsibilities: The PI and site investigators will agree to implement the IRB approved protocol and conduct the study in accordance with Section 9 (Commitments) of FDA form 1572, Title 21 of the US CFR, and the ICH GCP Guidelines (E6, Section 5) as well as all national, state and local laws of applicable

Regulatory Authorities. 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 requirements.

R. Study Limitations:

The study is a multi-center trial with the potential for variation in prehospital standard of care and in-hospital variation in post-injury care potentially affecting the primary and secondary outcomes for the proposal. We elected to standardize prehospital emergency medical standard of care to minimize any prehospital variability. Importantly, we selected similar academic, level 1, participating centers based upon their patient and emergency medical transport volumes, there prior experience with clinical research and prior participation in prior multi-center trials, and who practice up-to-date evidence based trauma care, in attempts to minimize significant variation in post injury care.

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Clinical Protocol Appendix 2

Proposed Community Consultation and Public Disclosure Plan STAAMP Trial

I. Community Consultation

A. City of Pittsburgh

1. Consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn

B. Website

Information about the current STAAMP Trial will be posted on a website which has been developed for this purpose. Contact information will be provided for questions and comments. All multimedia material will have the following website listed: www.acutecareresearch.org
There will be information on how to get more information about the trial and how to obtain on "opt out bracelet" if desired.

C. Surveys

Paper surveys will be placed in the Trauma Service outpatient clinic. They will also include the web address and contact information. A detailed telemarketing survey will be performed over a four-week period with approximately 500 households in the zip codes we intend to conduct this study.

D. Presentation to Pennsylvania Emergency Health Services Counsel

We will schedule to present at one of their meetings

II. Public disclosure

A. Multi-Media

The UPMC Media Office will issue a press release describing the upcoming study and locations of public forums.

B. Notifications will be posted on our local Pittsburgh Authority public transportation buses. The website address will be posted. Contact information will be provided for questions and comments. This will

include information regarding how to obtain an opt-out bracelet. This has been the most effective means of getting feedback in our area.

C. Flyers
We will distribute flyers directing traffic to our local website. Flyers will be provided in hospital waiting areas and community bulletin boards.

D. Presentation to local paramedics, emergency physicians, and medical directors

E. E-mail listserv
We will create an e-mail listserv using Campaign Monitor and will add community members that express interest in our research based on e-mails, calls, inquiries, and referrals.

F. Opt out bracelets will be made available upon request. They will be orange and state “NO STAAMP”.

Clinical Protocol Appendix 3 – Data Safety Monitoring Board (DSMB) Charter

DSMB Charter

Study of Tranexamic acid during Air and ground Medical Prehospital transport (STAAMP) trial

August 03, 2017

Version 1.3

Data Safety Monitoring Board (DSMB) Overview

Trial Description and Study Design

- Trial name: Study of Tranexamic acid during Air and ground Medical Prehospital transport (STAAMP) trial
- Principal investigator (PI): Jason Sperry, MD, MPH
- Funding agency: Department of Defense
- Trial design: Multi-center, prospective, randomized, blinded, controlled interventional trial.
- Phase: III
- Number of patients: 994
- Number of sites: 4

DSMB Description

- This DSMB will be coordinated by the PI, Jason Sperry, MD, MPH.
- This DSMB will be independent of the investigators, funding agency, regulatory agencies, and institutional review boards.
- This charter will be approved by its DSMB members as attested to by signature of the chairperson.

DSMB Membership

- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest in accordance with provisions in this charter.
- DSMB members will sign confidentiality agreements covering DSMB activities.
- Composition of membership will be researchers with the following expertise: hematology (transfusion medicine), surgery (trauma/critical care), prehospital emergency medicine, epidemiology (clinical trial design), and biostatistician.
- Remuneration will be provided any expenses related to DSMB activities.

Reporting

- Unblinded data to be reviewed by the DSMB will be provided by an independent statistician. Issues and recommendations identified by the DSMB will be provided to the principal investigator by the DSMB chairperson in accordance with this charter.
- Details of closed session deliberations (e.g., minutes) will be considered privileged and not subject to disclosure except as required by law.

Introduction

The purpose of this charter is to define the roles and responsibilities of the DSMB, delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DSMB will function in accordance with the principles of the following documents: FDA document "Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees".

Study Overview/Summary

Objective/Hypothesis: The primary hypothesis will be that prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of 30 day mortality. The secondary hypotheses include that prehospital tranexamic acid will reduce the incidence of hyperfibrinolysis, acute lung injury, multiple organ failure, nosocomial infection, mortality, early seizures, pulmonary embolism and early resuscitation needs, reduce or prevent the early coagulopathy as demonstrated by improving presenting INR and rapid thromboelastography parameters, reduce the early inflammatory response, plasmin levels, leukocyte, platelet and complement activation, and determine the optimal dosing of tranexamic acid post-injury..

Specific Aims:
Aim#1: Determine whether prehospital tranexamic acid as compared to placebo results in a lower incidence of 30 day mortality, 24 hour mortality, acute lung injury, multiple organ failure, nosocomial infection and improved shock parameters and early resuscitation and transfusion requirements.

Aim#2: Determine whether prehospital tranexamic acid as compared to placebo reduces hyperfibrinolysis, lowers the incidence of acute traumatic coagulopathy and improves early markers of coagulopathy.

Aim#3: To explore novel mechanisms by which prehospital tranexamic acid alters the inflammatory response independent of effects on hyperfibrinolysis including analysis of platelet and leukocyte activation, plasmin levels and plasmin mediated complement activation and the early cytokine response to trauma.

Aim#4: Determine whether different dosing regimens of tranexamic acid upon arrival in the hospital are associated with improvements in hyperfibrinolysis, coagulopathy, clinical outcomes and the early inflammatory response.

Study Design: Multi-center, prospective, randomized, blinded, controlled interventional trial over 3 years focusing on patients with concern for bleeding who are transported via air medical transport to definitive care.

Population: Blunt or penetrating injured patients transported via emergency medical transport within two hours of injury with concern for bleeding with 1.) a documented systolic blood pressure < 90 mmHg en route at outside/referral facility AND 2.) documented tachycardia (> 110 bpm) en route or at outside/referral facility..

Inclusion Criteria:

1. Blunt or penetrating injured patients being transported via emergency medical services from the scene of injury or from referring hospital to a definitive trauma center that is participating in the trial
AND
2. Within 2 hours of time of injury
AND
3A. Hypotension (Systolic Blood Pressure (SBP) < 90mmHg)
    i. At scene of injury or during emergency medical transport
    ii. Documented at referring hospital prior to emergency medical transport arrival
OR
3B. Tachycardia (heart rate >110 beats per minute)
    i. At scene of injury or during emergency medical transport
    ii. Documented at referring hospital prior to emergency medical transport arrival
    Inclusion criteria #3. and #4. not required to be simultaneous

Exclusion Criteria:
1. Age > 90 or < 18 years of age;
2. Inability to obtain intravenous or intraosseous access ;
3. Documented cervical cord injury with motor deficit;
4. Known prisoner;
5. Known pregnancy;
6. Traumatic arrest with > 5 minutes CPR without return of vital signs;
7. Penetrating cranial injury
8. Traumatic brain injury with brain matter exposed;
9. Isolated drowning or hanging victims
10. Wearing an opt out bracelet.
11. Isolated fall from standing
12. Objection by patient or family member

Interventional Arm: The Intervention will have both a prehospital phase and in-hospital phase. Investigational Drug Services (IDS) at the University of Pittsburgh will be utilized to supply and organize both tranexamic acid and placebo along with respective normal saline bolus and infusion bags to all participating trial sites. IDS at the University of Pittsburgh has a long track record of managing large multicenter trials and is currently executing and responsible for over 150 inpatient and outpatient clinical trials.

Prehospital Phase Intervention: Once inclusion and exclusion are verified while the patient is being transported via emergency medical transport to a STAAMP trial participating center, in a randomized, double blinded fashion, either 1 gram bolus of tranexamic acid diluted in 100cc of normal saline (preprepared on helicopter) or placebo of identical volume will be infused into the patient over approximately 10 minutes. After receiving the prehospital phase intervention, standard operating procedures utilizing goal directed crystalloid infusion will be followed

In-hospital Phase Intervention: Upon arrival, patient blood and labs will be sampled and arrival rapid-TEG analysis will be performed within first 60 minutes. After inclusion and exclusion criteria verification by research staff, in a double blinded, randomized fashion, those patients who received tranexamic acid in the prehospital phase will receive 1 of 3 different dosage regimens:

1. *Standard Tranexamic acid Dosing*: 1 gram infusion over 8 hours

2. *Repeat Tranexamic acid Dosing*: 1 gram bolus and 1 gram infusion over 8 hours
3. *Abbreviated Tranexamic acid Dosing*: No further tranexamic acid to be given

For intervention blinding purposes, each patient will receive both a bolus dose (either tranexamic acid or placebo) and 8 hour infusion (either tranexamic acid or placebo) depending on the randomized dosing regimen.

Placebo/Control Arm: Prehospital phase patients randomized to placebo will receive identical placebo diluted in 100cc of normal saline and infused over 10 minutes. Patients who received prehospital phase placebo will receive in-hospital identical placebo bolus and 8 hour placebo infusion for blinding purposes

Randomization: The randomization scheme will have both a prehospital phase and in-hospital phase.

Prehospital Phase Randomization: Individual patients meeting criteria while en route via emergency medial transport will be randomized using an allocation sequence block size of 8 to either 1 gram of tranexamic acid or placebo diluted in 100cc of normal saline given over 10 minutes. A single prehospital treatment box containing ascending numerically labeled (1-8) treatment packs (randomized with a computer random number generator) will be on board each respective emergency transport vehicle. In an ascending numerical order fashion treatment packs will be utilized for enrolled patients. The box and treatment pack # will be recorded by research staff upon arrival for all randomized patients. The patient and all treatment and research staff will be blinded to the treatment arm. All intervention vials will be covered to obscure view of vial contents to prehospital staff giving the intervention and amber colored syringes will be utilized to maintain blinding. IDS at the University of Pittsburgh will be unblinded to the prehospital intervention. Additionally, the pharmacy at each respective participating center will have access to the prehospital randomization/assignment scheme once the prehospital intervention box and treatment # are provided to them by the accepting research staff at each participating center.

In-hospital Phase Allocation: Using a web based, randomization assignment program built specifically for the trial, research staff will provide and input the prehospital intervention box # and treatment pack # into the web based platform at each site and be provided the In-hospital treatment allocation to be utilized for the second phase intervention. IDS at the University of Pittsburgh and each respective pharmacy at the participating sites will be provided with the random allocation sequence and will be unblinded to the in-hospital allocation assignment. The accepting research staff and pharmacy will verify they have the same in-hospital phase treatment assignment as an additional check to the allocation assignment. An allocation sequence based upon a block size of 9 again generated with a computer random number generator will be utilized for those who received prehospital Tranexamic Acid. Each respective IDS or pharmacy will prepare the inhospital phase treatment (10 minute and 8 hour infusion). The patient and all treatment and research staff will be blinded to the treatment that is received.

Blinding: The trial is a double blinded trial for both the prehospital phase and in-hospital phase interventions. The participants, investigators, research coordinators and staff, and persons having any contact with the patients will be blinded to study treatment assignments. The IDS at the University of Pittsburgh will be unblinded to the prehospital phase treatment arm and the respective pharmacy at each center will be unblinded once the treatment prehospital treatment information is

provided to them by research staff. Both IDS at the University of Pittsburgh and the respective IDS or pharmacy at each center will be unblinded to the in hospital treatment assignment.

Roles and Responsibilities

DSMB Roles and Responsibilities

This DSMB will

- Meet periodically (see DSMB Meetings) to review aggregate and individual subject data related to safety, data integrity and overall conduct of the trial.
- Review specific interim analyses for efficacy (see Study Review Criteria/Stopping Rules and Guidelines).
- Provide recommendations to continue or terminate the trial depending upon these analyses.
- Communicate other recommendations or concerns as appropriate.
- Operate according to the procedures described in this charter and all procedures of the DSMB.
- Follow conflict of interest guidelines as detailed below (see DSMB Membership).
- Comply with confidentiality procedures as described below (see Confidentiality).
- Maintain documentation and records of all activities as described below (see DSMB Meetings, DSMB Reports).

Principal Investigator (or Designees) Roles and Responsibilities

The PI will directly or through delegation:

- Assure the proper conduct of the study.
- Assure collection of accurate and timely data (monitoring and data management).
- The PI will designate an independent statistician to compile and report SAEs to the DSMB.
- Promptly report potential safety concern(s) to the DSMB.
- Prepare summary reports of relevant data for the DSMB. (This may include analyses not otherwise outlined in this charter based upon findings.)
- Provide an independent facilitator for presentation of results during DSMB meetings if requested by the DSMB.
- Communicate with regulatory authorities, IRB, and investigators, in a manner that maintains integrity of the data, as necessary. (This communication is not the responsibility of the DSMB.)
- Provide funding for the study and DSMB.
- PI will not attend the closed session of the DSMB Meeting.

DSMB Membership

The DSMB will consist of at least 4 members. The DSMB members have been selected by the PI in consultation with the investigators.

As characteristic qualifications, members will:

- Work professionally and meet qualifications for their respective professions.
- Comply with accepted practices of their respective professions.
- Comply with the conflict of interest policies specified by the standard operating procedures (SOPs) of the PI to ensure that members do not have serious scientific, financial, personal, or other conflicts of interest related to the conduct, outcome, or impact of the study according to

the guidelines specified below (e.g., engaged in any simultaneously occurring competitive trials in any role that could pose a conflict of interest for this study).

- Be independent from the PI, IRB, regulatory agencies, principal investigator, co-principal or sub-principal investigator, site investigator, site sub-investigator, clinical care of the study subjects, or any other capacity related to trial operations.
- Not be on the list of Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) (http://www.fda.gov/foi/nidpoe/default.html) and/or debarred list of investigators (http://www.fda.gov/ora/compliance_ref/debar).

Although each DSMB member will be expected to serve for the duration of the trial, in the unlikely event that a member is unable to continue participation, the reason will be documented and a replacement will be selected by the PI.

The DSMB will follow conflict of interest guidelines referenced by the Department of Health and Human Services, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection (http://www.hhs.gov/ohrp/humansubjects/finreltnn/fguid.pdf). DSMB members will sign a non-conflict of interest statement in regard to this study which will be on file with the PI. As determined by the PI, conflicts of interest and/or potential conflicts of interest (as determined by SOPs) will be reduced to the greatest extent that is consistent with assembling a highly competent DSMB. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DSMB chairperson with input from other DSMB members and PI as necessary.

DSMB Meetings

Projected Schedule of Meetings

An initial meeting of the DSMB will be held prior to any subject enrollment in the study in order for the members to review the charter, to form an understanding of the protocol and definitions being used, to establish a meeting schedule, and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data (adverse events, protocol deviations, enrollment summary and tables for overall primary and secondary endpoints). Frequency of meetings will be every six months, unless the board determines otherwise.

Meeting Format

DSMB meetings will generally be conducted by teleconference and coordinated by the PI. A quorum, defined as 2 out of 4 members will be required to hold a DSMB meeting. Critical decisions of the DSMB should be made by unanimous vote. However, if this is not possible, majority vote will decide.

Open and Closed Sessions

The open session may be attended by the PI and study investigators or their designees. Data presented in the open session may include enrollment data, individual adverse event data, baseline characteristics, overall data accuracy and compliance data or issues, and other administrative data. Minutes of the open session will be recorded by the Chair of the DSMB. Minutes will be finalized upon signature of the chairperson and maintained by the DSMB in accordance with applicable statutory regulation.

The closed session will be restricted to the DSMB members. A facilitator or recorder may be requested by the DSMB. Data which may compromise the integrity of the study (e.g., comparative

data) will be analyzed and discussed only in the closed session. The minutes of the closed session will be recorded by the DSMB Chair. Minutes from the closed session will be recorded separately from the minutes of the open session and stored securely by the DSMB Chair. Closed session minutes, finalized by signature of the chairperson, will be maintained in confidence and retained until discarded in accordance with applicable statutory regulation.

Following each meeting, a report separate from the minutes of the open and closed sessions will be sent to the PI describing the DSMB recommendations and rationale for such (see DSMB Communication of Findings and Recommendations).

Study Review Criteria/Stopping Rules and Guidelines

Guidance for the conduct of safety and efficacy analyses, and guidelines / stopping rules will be established prior to the DSMB's first evaluation of data.

Safety Analyses

The primary safety endpoint is mortality as observed during interim analysis. In addition to the primary safety endpoint, the DSMB will monitor the following adverse events:

1. Acute Lung Injury
2. Nosocomial infection
3. MOF (multiple organ failure)
4. Early seizures
5. In-hospital pulmonary embolism
6. Blood and blood component transfusion and resuscitation requirements
7. Adverse Events
8. Unexpected Adverse Events
9. Expected Adverse Events

Stopping Guidelines / Stopping Rules: Safety

Termination or modification may be recommended for any perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary endpoint resulting in adverse events, or unexpected SAEs.

Efficacy Analyses

The primary outcome variable 30 day mortality will be utilized to access for efficacy of the trial. Accessing this primary outcome variable at each interim analysis will allow early termination of the trial for either lack of efficacy or excessive efficacy.

Adaptive Protocol Modification

There is no planned sample size re-estimation; however if the DSMB reveals a need, the sample size calculation can be re-evaluated.

Consideration of External Data

The DSMB will also consider data from other studies or external sources during its deliberations, if available, as these results may have a profound impact on the status of the patients and design of the current study.

DSMB Reports

Monitoring for Safety

The primary charge of the DSMB is to monitor the study for patient safety. Formal DSMB safety reviews will occur as specified above (see Study Review Criteria/Stopping Rules and Guidelines).

Monitoring for Efficacy
The DSMB will monitor efficacy outcomes to determine relative risk/benefit, futility, or for early termination due to overwhelming efficacy. Interim analyses efficacy reports sent to the DSMB will occur as specified above *(*see Study Review Criteria/Stopping Rules and Guidelines).

Monitoring for Study Conduct
The DSMB will review data related to study conduct. Data to be reviewed and listed in the DSMB reports includes: enrollment rates over time, time from last patient enrolled to date of report (indication of delay between treatment or follow-up and reporting), summary of protocol violations, and completeness of treatment and follow-up visit data.

Data Flow for Adverse Events
The DSMB will carefully monitor adverse events periodically throughout the duration of the study. This process will be dynamic to include quarterly reviews of all reported SAEs by the DSMB chairperson. The investigators will be expected to report Serious Adverse Events (SAEs) to the PI within 24 hours of knowledge of the event. The PI will then report it to the DSMB within 7 days.

Preparation of Reports to the DSMB
At the scheduled 6 month DSMB meetings, the study statistician will prepare results for the closed session that show outcomes by treatment effect but with the blinds intact. An independent statistician will prepare and distribute reports to the DSMB electronically approximately 7 days prior to the date of each DSMB meeting.

In order to provide the maximum amount of information to the DSMB, the analyses will employ the most recent data (recognizing limitations thereof) available at the time of the analysis. Requests for additional data by the DSMB members will be made to the DSMB chairperson or his or her designee, who will be responsible for communicating the request with the PI.

The DSMB will review the data and discuss the analyses during the closed portion of the scheduled meeting. If in the closed session the DSMB finds blinded results that are concerning, the meeting will be ended and the DSMB will reconvene in closed session within 1 week to be given the same data unblinded. If the meeting is necessary, an additional interim analysis will be added to the two scheduled interim analyses resulting in the need to recalculate alpha spent. We will be cognizant of the logistical and scientific costs associated with this plan when we are considering any unscheduled analysis.

For the interim analyses at 1/3 and 2/3 enrollment points, the biostatistician will create two reports for the DSMB closed session meeting: one with the treatment arms blinded and one with the blinds broken. The biostatistician will first present to the DSMB data with the blinds intact in closed session. If no point estimates are within the range of the *a priori* stopping rules, the statistician will be asked to proceed at that time with presenting a report with the blinds broken. As the alpha accounting for these two interim looks has already been calculated, it will not need to be recalculated.

DSMB Communication of Findings and Recommendations

Following each meeting and within 14 days of the meeting, the chairperson will send findings and recommendations of the DSMB in writing to the PI.

These findings and recommendations can result from both the open and closed sessions of the DSMB. If these findings include serious and potentially consequential recommendations that require immediate action, the chairperson will also promptly notify the PI by phone and/or by email.

PI's Response to DSMB Findings and Recommendations

The PI and co-investigators will review and respond to the DSMB recommendations. The recommendations of the DSMB will not be legally binding but require professional consideration by the recipients. If the DSMB recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the DSMB will request that the PI provide a formal written response stating whether the recommendations will be followed and the plan for addressing the issues.

It is recognized that the PI may need to consult with regulatory agencies or other consultants before finalizing the response to the DSMB. Upon receipt, the DSMB will consider the PI response and will attempt to resolve relevant issues, resulting in a final decision. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of the PI to manage the study, should the study continue. The PI will agree to disseminate the final decision to the appropriate regulatory agencies, IRB, and investigators within an appropriate time.

In the unlikely event of irreconcilable differences, especially regarding study termination or other substantial study modifications, the DSMB may decide to discontinue monitoring the current study and disband. This decision will be communicated to the PI, FDA, and IRBs.

Public disclosure of the PI's final decision or DSMB recommendations will be at the discretion of the PI or their designee. The DSMB will not make any public announcements either as a group or individually.

DSMB Closeout

This study may be terminated under a variety of circumstances including, but not limited to, termination for overwhelming effectiveness, futility, or safety issues per protocol or DSMB monitoring guidelines. Responsibilities of the DSMB with regard to closeout will be to review the final study report to ensure study integrity. The DSMB may recommend continuing action items to the PI based upon the final review.

Confidentiality

All data provided to the DSMB and all deliberations of the DSMB will be privileged and confidential. The DSMB will agree to use this information to accomplish the responsibilities of the DSMB and will not use it for other purposes without written consent from the study PI and co-investigators. No communication of the deliberations or recommendations of the DSMB, either written or oral, will occur except as required for the DSMB to fulfill its responsibilities. Individual DSMB members must not have direct communication regarding the study outside the DSMB (including, but not limited to the investigators, IRB, regulatory agencies, or PI) except as authorized by the DSMB.

Amendments to the DSMB Charter

This DSMB charter can be amended as needed during the course of the study. Information to be included as amendments will be any modifications or supplements to the reports prepared for the DSMB, as well as amendments to other information addressed in this charter. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the minutes of the DSMB meetings. Each revision will be reviewed and agreed upon by both the study PI and the DSMB. All versions of the charter will be archived in accordance with this document and maintained by the PI.

Clinical Protocol Appendix 4 – Stopping Rules

STAAMP Trial Stopping Rule and Data Monitoring

In concert with the DSMB, prior to initiation of the trial, the final monitoring plan will be developed to serve as the guide to the DSMB's decision-making process concerning early stopping of the trial monitoring safety and efficacy. In making the decision to recommend termination of the study, the DSMB shall be guided by several types of information: (i) a formal stopping rule based on the primary analysis (comparison of treatment groups on the 30 day mortality), (ii) information on safety outcomes by treatment group, (iii) consistency between results for primary and secondary outcomes, and (iv) consistency of treatment effects across subgroups.

1. **O'Brien-Fleming spending (z-values and related alpha) of interim boundaries for each look**

We have designed this trial with a two interim look before the final analysis. Our power analysis generated assuming a total of 3 sequential tests based on O'Brien-Fleming spending function to determine alpha spending and test boundaries. We will use test of proportions differences, two sided z-test with continuity correction applied and other adjusting techniques. The level of significance will maintain an overall p value of 0.05 according to O'Brien-Fleming stopping boundaries leaving a p value of 0.038; two sided, for the final analysis with a final z-value of 1.993. An independent data and safety monitoring board (DSMB) will periodically review the efficacy and safety data. DSMB will issue related recommendations based on comprehensive data monitoring and substantiated evidences. Two formal interim analyses of efficacy will be performed when 33% and 67% of the expected number of primary events had accrued (about one month after 1/3 and 2/3 of subject accruals). The purpose of our sequential tests is to detect early sign of superior efficacy and detect further apparent futility in the intervention group. This kind of futility monitoring and testing could cause this trial to be stopped as soon as a negative outcome of 30-days mortality is inevitable and thus it is no longer worthwhile continuing the trial to its completion. Such early termination for futility could reduce the enormous expenditures of resources, human and financial, involved in the conduct of trials that ultimately provides negative answers regarding the value of the study medical intervention.

Our trial's lower and upper stopping boundaries have been computed to ensure that the trial Type I and Type II error probabilities of the group sequential plan are according to the study assumptions and design. The upper boundaries are related to the formal efficacy testing at each assigned sample size (expected number of primary events completion at 33%, 67%, and 100%). The lower boundaries are related to the formal futility (safety) testing at each assigned sample size (expected number of primary events completion at 33%, 67%, and 100%). Upper and lower boundaries will be provided to DSMB as a guideline and could be modified by DSMB prior to the trial upon reasonable justifications. With this sequential testing plan based on O'Brien-Fleming spending function, only an absolutely overwhelming treatment intervention can justify the termination of our clinical trial after a third of the subjects have been enrolled and completed a one month of follow up. If the trial has been ordered to stop early because of interim analysis, adjusted p-values will be computed based on the described analysis of our main clinical outcome. Unadjusted p-value will not be considered for final results interpretations.

Our interim analysis is part of our three sequential testing as we have mentioned above. At each of the two interim looks, 30 days-mortality will be pooled across participated centers comparing between the two study groups. Based on the assumed power analysis at each interim look, the z-value will be calculated and checked against the upper and lower values guide lines for that specific check. We have illustrated z-values for the upper and lower boundaries across interim two analyses and final analysis of a total accumulated alpha of 0.05. (Figure and Table below)

Details when Spending = O'Brien-Fleming, N1 = 497, N2 =497, P1 = 0.10, P2 = 0.16

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	0.33	-3.71030	3.71030	0.000207	0.000207	0.000207	0.018687	0.018687
2	0.67	-2.51142	2.51142	0.012025	0.011890	0.012097	0.399207	0.417894

3	1.00	-1.99302	1.99302	0.046259	0.037903	0.050000	0.382494	0.800388

Drift 2.82089

Look: These are the sequence numbers of the interim tests.

Time: These are the time points at which the interim tests are conducted. This is also related to proportion of subject accruals

Lower and Upper Boundary: These are the test boundaries. If the computed value of the test statistic *z* is between these values, the trial should continue. Otherwise, the trial can be stopped.

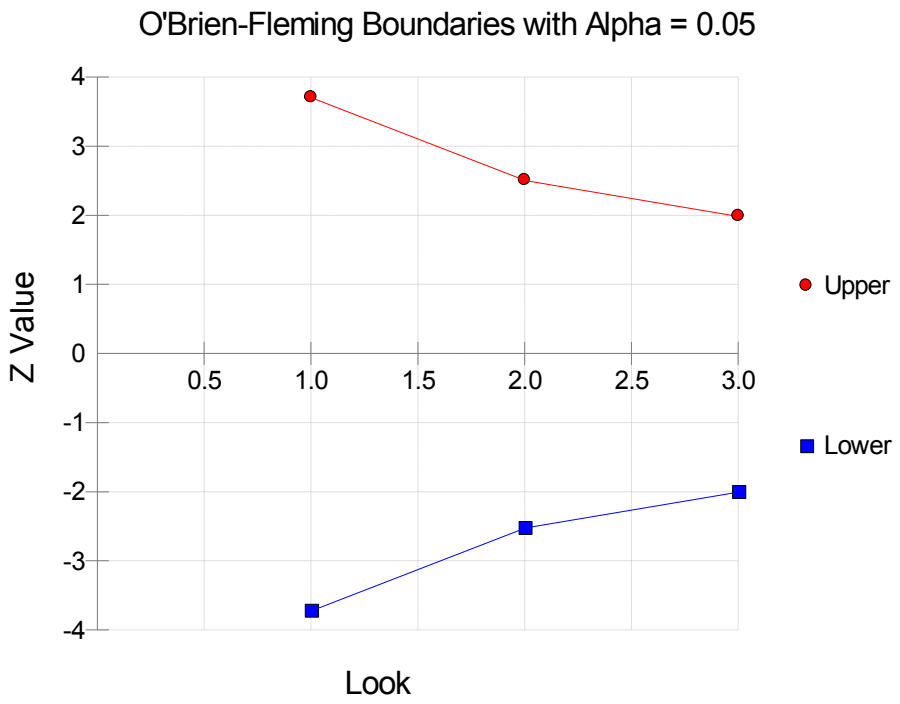
Nominal Alpha: This is the value of alpha for these boundaries if they were used for a single, standalone test. Hence, this is the significance level that must be found for this look in a standard statistical package that does not adjust for multiple looks.

Inc Alpha: This is the amount of alpha that is *spent* by this interim test. It is close to, but not equal to, the value of alpha that would be achieved if only a single test was conducted. The difference is due to the correction that must be made for multiple tests.

Total Alpha: This is the total amount of alpha that is used up to and including the current test.

Inc Power: These are the amounts that are added to the total power at each interim test. They are often called the exit probabilities because they give the probability that significance is found and the trial is stopped, given the alternative hypothesis.

O'Brien-Fleming boundary values are inversely proportional to the square root of information levels on the standardized Z scale (O'Brien and Fleming 1979). The O'Brien-Fleming boundary is conservative in the early stages and tends to stop the trials early only with a small P-value. But the nominal value at the final stage is close to the overall P-value of the design.



The above plot shows the interim boundaries for each look. This plot shows very dramatically that the results must be extremely significant at early looks, but that they are near the single test boundary (1.96 and -1.96) at the last look.

References

1. Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.
2. Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.
3. O'Brien, P.C. and Fleming, T.R. 1979. 'A multiple testing procedure for clinical trials.' Biometrics, 35, pages 549-556
4. Pocock, S.J. 1977. 'Group sequential methods in the design and analysis of clinical trials.' Biometrika, 64, pages 191-199

5. Reboussin, D.M., DeMets, D.L., Kim, K, and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

2. Eligibility, recruitment, and accrual reporting

Our periodic reports to DSMB will include as well data on recruitment, data completion, data quality, etc. Data will be summarized in tables as listed below of simplicity and clarity. For simplicity and clarity in reading information, data on eligibility, recruitment, and accrual reporting will be summarized in table 1 and figure 1 and 2.

Table 1 Recruitment and Accrual

	Center1		Center2		Center3		Center4		Center5		Total	
Study treatment	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Duration of time in weeks since start going life												
Number of Patients screened												
Number of patient eligible for study												
Eligible but not entered in the study												
Drop off / not able to follow up												
Total patient "randomized"												
Average accrual per month												
Data completion (✓)												
Data Quality (✓)												

Figure 2 Overall Accrual

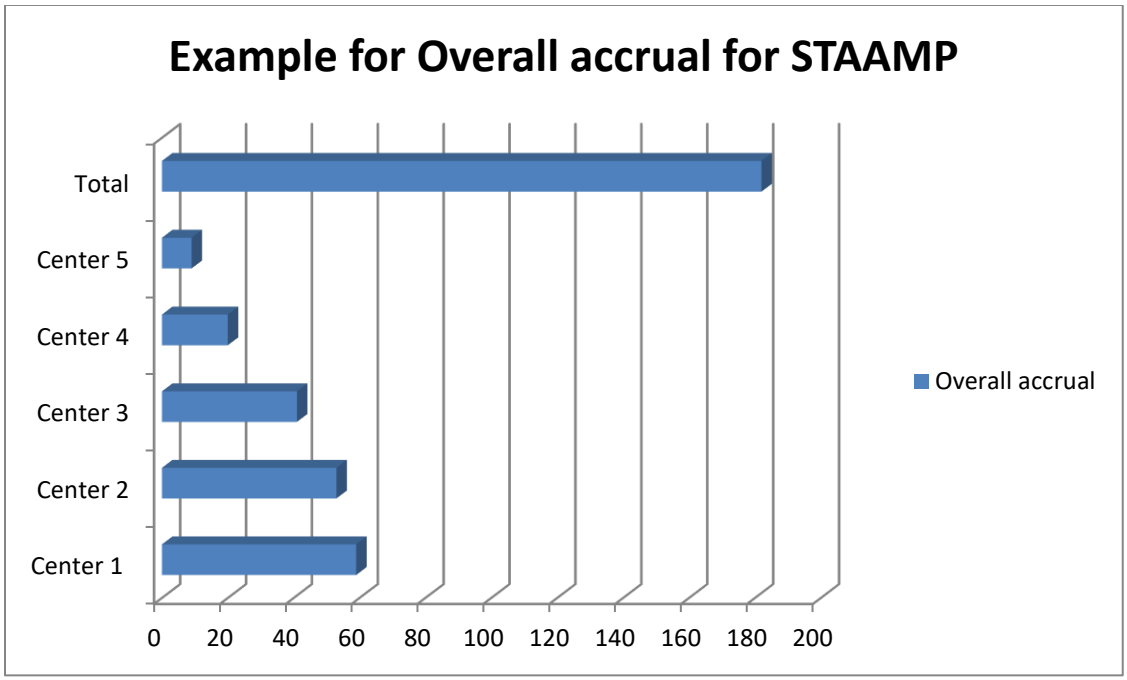
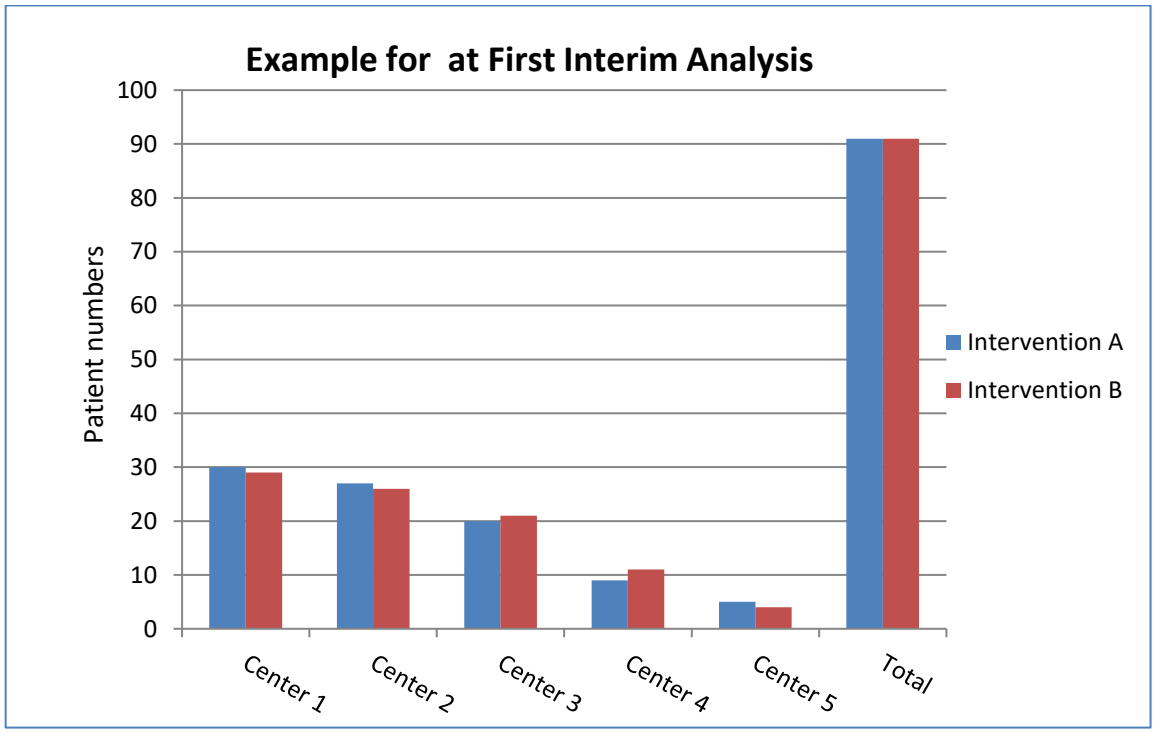


Figure 3 Accrual by intervention and centers



3. Information on subjects' demographics and illnesses

In details information on subjects' demographics and illnesses will be summarize in table 2

Table 2 Demographics and Baseline Disease Characteristics

	Center1		Center2		Center3		Center4		Center5		Total	
	A	B	A	B	A	B	A	B	A	B	A	B
Patients numbers												
Age, median and range												
Sex (male) n (%)												
Race, N (%) **White** **Black** **Other**												
Average Lowest pre hospital SBP												
Average Heart rate												
Average Perspiration Rate												
Median ISS												
Mechanism of Injury (blunt) (%)												
CPR (%)												
Pre hospital Blood transfusion (%)												
!!!												

4. Monitoring Safety and efficacy

Further and in relation to interim safety analysis, safety data by study groups labeled as Interventional group (Early using of tranexamic acid) and Control group (Standard of care) will be provided periodically to DSMB. These processed data will provide information on safety outcomes by treatment group, ascertain the consistency between results for primary and secondary outcomes, and inspect the consistency of treatment effects across subgroups. Safety data of the study include serious adverse events regarding frequency, anticipated or unanticipated, individual description for each event and dates. Other data will be provided as well as any additional safety analysis upon DSMB request. Mortality will be reported as an overall in our periodic reports (every 6-9 months depends on accrual rate) to DSMB however we will report mortality individually as treatment A and B at each of the trial two formal interim analyses. Data will be summarized in tables (3-6)

Table 3 Possible Adverse effects

	Center1		Center2		Center3		Center4		Center5		Total	
	A	B	A	B	A	B	A	B	A	B	A	B
Patients numbers												
Transfusion related lung injury n, (%)												
Allergic/anaphyl actic reaction												
Circulatory overload												
Infection												
Febrile reaction												
Hemolytic reaction												
!!!												
!!!												
!!!!												

Table 4 Unexpected Adverse Effects

	Center1		Center2		Center3		Center4		Center5		Total	
	A	B	A	B	A	B	A	B	A	B	A	B
Patients numbers												
1. n,(%)												
2.												
3.												
4.												

Table 5 Primary outcomes for patients in the Study

	Center1		Center2		Center3		Center4		Center5		Total	
	A	B	A	B	A	B	A	B	A	B	A	B
Number of Patients												
24 hr Mortality n, (%)												
30 day Mortality n, (%)												

Table 6 Secondary outcomes for patients in the Study

	Center1	Center2	Center3	Center4	Center5	Total

	A	B	A	B	A	B	A	B	A	B	A	B
Number of Patients												
Hyperfibrinolysis												
Acute lung injury (%)												
Multiple organ failure (%)												
Nosocomial infection (%)												
Improved shock parameters (%)												
Early resuscitation need (%)												
Transfusion requirements (%)												
Early seizures (%)												
Pulmonary embolism (%)												
Reduce or prevent the early coagulopathy as demonstrated by improving presenting INR (%)												
and Rapid thromboelastography parameters (%)												
Reduce the early inflammatory response, plasmin levels, leukocyte, platelet and complement activation (%)												
ICU days												
Ventilation days												
Hospital LOS												
!!!												