Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC): A Pilot and Feasibility Study (TIC-TOC Trial) PECARN Protocol Number 036

Pediatric Emergency Care Applied Research Network
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PROTOCOL TITLE:

Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children (TIC-TOC): A Pilot and Feasibility Study

Short Title: TIC-TOC Trial
PECARN Protocol Number: 036

Lead Investigators and Authors:
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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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1 Study Summary

This study is a Phase II, multi-center, randomized, double-blinded, placebo-controlled trial. It is a parallel arms design pilot trial randomizing 40 subjects.

1.1 Study Objectives

The primary objective of this pilot study is to collect preliminary data on the safety and efficacy of TXA in severely injured children. We will also assess the overall feasibility to potentially conduct a large, multi-center, clinical trial evaluating the benefit of TXA in children with significant hemorrhagic injuries. We will randomize subjects to one of three arms: 1) TXA dose A (low), 2) TXA dose B (high), or 3) placebo. (Figure 1 on the following page).

Specifically, the study objectives of this pilot and feasibility study are to:

- Provide preliminary data on the safety and efficacy of TXA in severely injured children with torso and/or head injuries;
- Evaluate the ability to efficiently screen, identify, consent, randomize, and initiate study intervention within 3 hours of injury;
- Demonstrate the ability to measure and complete 48-hour (blood product transfusion requirements) and early and long-term (global neurocognitive functioning) outcomes;
- Evaluate the proportion of subjects with the outcomes of interest with the current inclusion/exclusion criteria;
- Assess protocol adherence and variability of care in randomized subjects; and
- Identify operational efficiencies and inefficiencies with the potential to enhance the success of the subsequent clinical trial

1.2 Outcome Measures

This pilot study is not powered for a confirmatory test of efficacy or safety of TXA. To provide preliminary data on safety and efficacy and to evaluate our ability to reliably determine clinical outcomes, we will collect the following data in this pilot trial:

1. The total amount of blood products transfused (packed red blood cells, plasma, platelets, and cryoprecipitate in mL/kg) in the initial 48 hours following randomization,

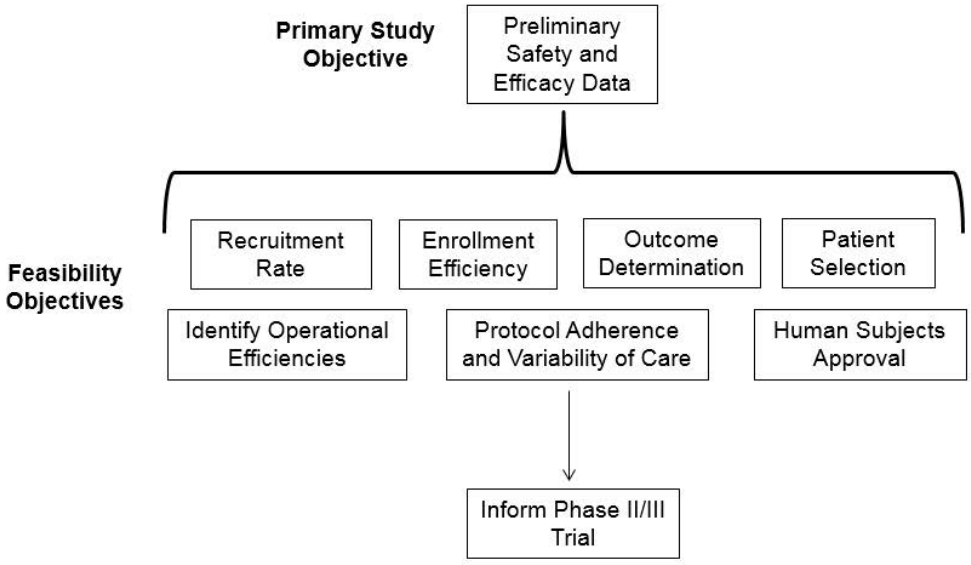


Figure 1: Schema of Study Objectives

2. Intracranial hemorrhage progression at 24 hours (plus or minus 6 hours),
3. Global functioning, specifically Pediatric Quality of Life (PedsQL) and Pediatric Glasgow Outcome Scale Extended (GOS-E Peds) scores at 1 week, 1 month, 3 months, and 6 months,
4. Short term memory (digit span test),
5. Adverse events, specifically thromboembolic (TE) events and seizures.

1.3 Subject Eligibility, Accrual and Study Duration

Children younger than 18 years with evidence of hemorrhagic injuries to the torso or brain will be eligible. Eligible subjects will be divided into three groups (head injury, torso injury, or head and torso injury) based on inclusion criteria below. Subjects in the combined head and torso injury group must meet entry criteria for both head and torso trauma.

1.3.1 Inclusion Criteria

Inclusion criteria are:

1. Less than 18 years old AND

   Penetrating Torso Trauma:

2. Penetrating trauma to the chest, abdomen, neck, pelvis, or thigh with at least one of the following:
   - age-adjusted hypotension, or
   - age-adjusted tachycardia despite adequate resuscitation fluids, or
   - radiographic evidence of internal hemorrhage, or
   - clinical suspicion of ongoing internal hemorrhage, OR

   Blunt Torso Trauma:

3. Clinical suspicion of hemorrhagic blunt torso injury and at least one of the following:
   - age-adjusted hypotension, or

- persistent age-adjusted tachycardia despite adequate resuscitation fluids, OR

4. Hemothorax on chest tube placement or imaging; OR
5. Clinical suspicion of hemorrhagic blunt torso injury and intraperitoneal fluid on abdominal ultrasonography (Focused Assessment with Sonography in Trauma; FAST); OR
6. Intra-abdominal injury on CT with either contrast extravasation or more than trace intraperitoneal fluid; OR
7. Pelvic fracture with contrast extravasation or hematoma on abdominal/pelvic CT scan with at least one of the following:
   - age-adjusted tachycardia or
   - age-adjusted hypotension, OR

Head Trauma:

8. GCS score less than or equal to 13 with associated intracranial hemorrhage on cranial CT scan (enroll after CT scan)

Determination of age

Patients younger than 18 years at the time of enrollment are eligible for the study. Age will be determined from the patient, relative, friend or the EMS personnel. In cases where age is not known, an estimation of age by the treating clinician will be used to determine eligibility.

Determination of time of injury

Time of injury may be provided by the subject, relative, friend, witness, EMS personnel, or any other treating provider. An estimation of the time of injury is acceptable. If conflicting reports on the time of injury exist, the time that may be viewed as the most reliable will be used. If the time of injury is unknown, the subject is not eligible for enrollment. Patients are excluded if the first dose of the study drug will be unable to be administered within 3 hours of the traumatic event.

Age-adjusted hypotension

This will be determined by accepted guidelines for vital signs in children.

Penetrating trauma

This will include stab wounds, gunshot wounds, or other objects that have penetrated the dermis.

Intra-abdominal injury
This will include any injury to the spleen, liver, kidney, gastrointestinal tract, or intraabdominal vessels.

Intraperitoneal fluid on abdominal ultrasound
This is defined as any fluid identified in the right upper quadrant (Morisons pouch), left upper quadrant or pelvis on the FAST examination.

Glasgow Coma Scale (GCS score)
Patients with GCS scores less than or equal to 13 and evidence of intracranial hemorrhage on cranial CT scan will be eligible for enrollment. The GCS scoring scale has a high sensitivity and excellent inter-rater reliability among physicians of multiple disciplines and nursing staff.[1, 2] In subjects who are preverbal (younger than 2 years), we will use the pediatric GCS score.[3] In subjects who are intubated and a verbal score cannot be assessed, we will use a predicted verbal score that has been previously validated.[4]

Intracranial hemorrhage on initial cranial CT
This will include any of the following findings: subdural hematoma, intraventricular hemorrhage, or intraparenchymal (cerebral) hematoma/hemorrhage/contusion. Intracranial hemorrhage can be due to either blunt or penetrating trauma.

1.3.2 Exclusion Criteria

Exclusion criteria include any of the below:

1. Unable to administer study drug within 3 hours of traumatic event
2. Known pregnancy
3. Known prisoners
4. Known wards of the state
5. Cardiac arrest prior to randomization
6. GCS score of 3 with bilateral unresponsive pupils
7. Isolated subarachnoid hemorrhage, epidural hematoma, or diffuse axonal injury
8. Known bleeding/clotting disorders
9. Known seizure disorders
10. Known history of severe renal impairment
11. Unknown time of injury
12. Previous enrollment into the TIC-TOC trial

13. Prior TXA for current injury
14. Non-English and non-Spanish speaking
15. Known venous or arterial thrombosis

Known pregnancy

This will be identified by history, physical examination or positive pregnancy test (if done prior to randomization) in females of child-bearing age. TXA is FDA pregnancy category B (Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women). Given the overall safety profile of TXA in pregnancy, we will not mandate checking pregnancy testing prior to enrollment but will stop study drug if pregnancy is identified. Prior studies of TXA use in pregnancy have demonstrated no increase in thromboembolic complications.[5–7]

Known prisoners

This will be identified by police or prison guards with patient.

Known wards of the state

These patients will be excluded per federal regulations (21 CFR 50.56).

Cardiac arrest

This will be defined as loss of pulses requiring chest compressions prior to randomization. Patients believed to have inappropriately received chest compression (in the presence of cardiac activity) are still eligible.

GCS score of 3 with bilateral non-reactive pupils

Our pilot data suggests that these patients have a mortality rate close to 100% and thus are unlikely to benefit from TXA.

Isolated subarachnoid hemorrhage, epidural hematoma, or diffuse axonal injury

Due to the clinical course of patients with these isolated traumatic intracranial hemorrhage subtypes, these patients are unlikely to benefit from administration of TXA.

Bleeding/clotting disorders

Patients will be excluded if they are known to have a bleeding or clotting disorder including hemophilia, prior episodes of DVT/PE or are on anticoagulants (e.g. warfarin).

Known seizure disorders

Patients will be excluded if they are known to have a seizure disorder and are currently

on medications for a seizure disorder. A history of febrile seizures is not considered a seizure disorder. Patients who have had a prior seizure but are not currently on long-term anti-seizure medication are eligible.

Severe renal impairment
Patients with impaired renal function may experience an increased elimination half-life for TXA. Thus patients with known severe renal impairment (creatinine clearance less than 29 mL/min/1.73m2) will be excluded. Similarly, if severe renal impairment is noted on baseline or subsequent laboratory measurements then drug discontinuation rules will be initiated. Patients with hepatic impairment will not be excluded. TXA is excreted unchanged and thus dose adjustment due to hepatic impairment is not recommended. Additionally, any elevations of hepatic enzymes or coagulation profile are more likely to be secondary to the patients traumatic injury and coagulopathy rather than due to the use of TXA.

Repeat enrollment of subjects
Although we anticipate subjects are unlikely to present with multiple episodes of severe trauma, a subject is only eligible to be enrolled into the study once.

Already received TXA for current injury
If the patient already received TXA for the current injury (pre- or in-hospital) they are not eligible for the study.

Known venous or arterial thrombosis
We will exclude patients with known venous or arterial thrombosis.

2 Rationale and Background

2.1 Traumatic coagulopathy and hyperfibrinolysis increases morbidity and mortality after pediatric trauma

Trauma is the leading cause of morbidity and mortality in children in the United States.[8] Deaths in children with trauma are primarily from direct injury to critical organs (brain, heart, lungs) or hemorrhage into the thoracic and/or abdominal cavities. In the initial 24 hours after injury, hemorrhage is the leading cause of death.[9] The degree of hemorrhage is influenced by both the extent of injury to the structures and the occurrence of trauma-induced coagulopathy. Traumatic coagulopathy is common after severe injury, particularly in patients with brain injuries, acidosis, and/or shock and independently

increases morbidity and mortality.[10–13] Nearly 30% of injured children admitted to the hospital have abnormalities of routine clotting parameters (INR and PTT) and 6% have markedly abnormal values.[14]

Hyperfibrinolysis, or the premature and excessive breakdown of blood clots, is a major component of traumatic coagulopathy.[15] As measured by thromboelastography (TEG) testing, hyperfibrinolysis has been shown to be present in 24% of severely injured children and increases the risk for death six-fold compared to children without hyperfibrinolysis.[16] Hyperfibrinolysis is also associated with the need for life-saving interventions and the need for blood product transfusions in severely injured children.[17]

2.2 Targeting fibrinolysis may attenuate post-traumatic hemorrhage and decrease blood product transfusion requirements

Tranexamic acid (TXA) is an antifibrinolytic lysine analogue that blocks the conversion of plasminogen to plasmin. Plasmin is central to fibrinolysis as it is the enzyme catalyzing the dissolution of fibrin clots. Thus, the administration of TXA prevents the formation of plasmin thereby preventing fibrin clot breakdown. Premature and excessive fibrinolysis is a primary component of traumatic coagulopathy and hemorrhage progression due to elevated levels of tissue plasminogen activator (t-PA) commonly seen after traumatic injuries, particularly TBI.[18]

Recent evidence in injured adults indicates that treatment with TXA decreases mortality and blood-transfusion requirements following traumatic hemorrhage.[19] The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial randomized 20,211 adult trauma patients at risk for significant hemorrhage to TXA or placebo. If administered within 3 hours of injury, TXA reduced the risk of death from bleeding by approximately one-third.[20] Furthermore, TXA had an excellent safety profile and was found to be cost-effective for use in these injured adult trauma patients.[21] Based on the results of the CRASH-2 trial, administration of TXA is considered standard-of-care for severely-injured adults with hemorrhagic trauma and is included on the World Health Organizations list of essential drugs.

Because TXA attenuates hemorrhage, it has the potential to improve clinically-important outcomes after TBI. Two phase-II clinical trials in adults with TBIs demonstrated a trend towards decreased intracranial hemorrhage progression with TXA use, and decreased mortality and improved functional outcomes.[22–24] The promising results of these trials led to the start of two large-scale, phase III trials, evaluating the use of TXA for adults with TBI.[25, 26]

2.3 TXA has not been appropriately studied in children with hemorrhagic injuries

Unfortunately, applying results of adult studies to children is inappropriate for several reasons. Children differ from adults with regards to anatomy, physiology, psychological development, mechanisms of injury and outcomes. Data regarding TXA use in children is mostly limited to those undergoing certain elective surgeries, specifically cardiac surgery,[27–29] with some small studies in children undergoing spinal and craniofacial surgeries.[30] These data suggest that perioperative administration of TXA decreases blood transfusion requirements in children.[27–30] Furthermore, these studies suggest an excellent safety profile for TXA use in children. The type of traumatic insult and degree of inflammation and its impact on coagulation in these elective surgeries, however, is likely different than that following hemorrhage from multisystem trauma.

One retrospective study evaluated the impact of TXA administration in children injured in Afghanistan. After controlling for injury severity, TXA substantially reduced mortality (odds ratio = 0.28, 95% CI 0.09, 0.89).[31] Unfortunately, only 66 (9%) of the 766 children in the database actually received TXA. Of note, there were no differences in venothromboembolic events between those who did and did not receive TXA.

Based on the TXA studies in injured adults, the evidence of safety and effectiveness in children undergoing non-traumatic surgical procedures and the limited study of TXA in injured children, there is great potential that TXA may safely reduce blood transfusion requirements (and morbidities) in injured children. Not surprisingly, determining if TXA is beneficial and safe in injured children is a top priority for numerous stakeholders.[32–34]

3 Study Design and Data Collection

3.1 Study Design Overview

This pilot study is a double-blind, randomized controlled trial of children younger than 18 years old with hemorrhagic injuries to the torso or brain. Children will be randomized to one of three arms: 1) TXA dose A (15 mg/kg bolus dose over 20 minutes, followed by 2 mg/kg/hr infusion over 8 hours), 2) TXA dose B (30 mg/kg bolus dose over 20 minutes, followed by 4 mg/kg/hr infusion over 8 hours), and 3) normal saline placebo. The pilot study will be conducted at 4 sites. This pilot study will be conducted in preparation for a subsequent phase II/III seamless clinical trial of TXA administration for children with hemorrhagic torso or brain injuries.

We plan to enroll 40 subjects (approximately 1.25 subjects per month at each of the 4 participating sites). The participating sites evaluate up to 10 subjects with significant

torso and cranial trauma monthly at their sites, therefore enrolling 1-2 per month at each site should be feasible.

3.2 Participant Screening and Consent

Subjects will be identified and recruited in the EDs of all participating centers. Potentially eligible subjects will be screened by the clinical research coordinators. Subjects believed to be eligible will be discussed with the treating physicians and the study site investigative team (clinician determined by each site and may include Site PI or Co-Investigators) to confirm eligibility. See section 7.2 and 7.3 for details of the consent process.

3.2.1 Missed Eligible Subjects

To assure that trauma patients recruited into this study are representative of the overall trauma population a review of the trauma admission log/trauma database may be conducted routinely during the screening and enrollment period of the trial. If a potential study participant met eligibility criteria but was not approached, the research coordinator will retrospectively complete a form with some basic demographic and clinical information on these patients. This will help assess potential enrollment bias. The Site PI will then discuss these cases with the nursing staff, as well as both the attending trauma and emergency physicians who failed to identify the patient as eligible for the study, as an opportunity to improve future enrollment.

3.3 Baseline Data Collection

Baseline data recorded for all children will include age, sex, race and ethnicity, and any other chronic medical conditions. At presentation to the ED we will also record vital signs and physical examination findings. We will also collect baseline laboratory values that are routinely collected as standard of care. To obtain information on fibrinolysis, we will also perform viscoelastic coagulation testing using thromboelastography (TEG). TEG testing is the only research-related lab testing per study procedures.

Demographics and injury characteristics will be collected (e.g., mechanism of injury, subject demographics, clinical information, and outcome).

Laboratory Data (collected if completed as standard of care procedures)
Examples of data elements:

- Creatinine
- CBC

- INR/PT

Baseline Clinical Information
Examples of data elements:

- GCS score (or Pediatric GCS score for those younger than 2 years-old)
- Pupillary assessment
- Vital signs
- Presence of and types of traumatic brain injuries, abdominal injuries, thoracic injuries, pelvic injuries, and orthopedic injuries

3.3.1 Biomarker testing

We will collect blood samples for TEG and other biomarker tests prior to the start of study drug infusion (baseline) and throughout the infusion. The results of the biomarker testing will be used for research purposes only and not be available to clinicians. The amount of blood drawn at each blood draw will be no more than 5-10 mls, or approximately one to two teaspoons of blood per blood draw. This is well below the maximum allowable volume (ml) of blood drawn for research purposes in children (5% of total blood volume).

Thromboelastography (TEG) testing Fibrinolysis is evaluated based on the percentage of clot lysis at 30 minutes post-maximum clot strength (LY-30) (Figure 2). The TEG testing will also provide information on coagulation factor function (clot time [r-value] and rate [k-time and alpha-angle]), and platelet function (maximum clot strength [maximum amplitude]). The TEG testing will be completed as soon as possible after enrollment into the study by the trained site-specific staff. All sites have verified TEG testing availability and processing time.

Although no studies have demonstrated an association between TEG directed management in injured patients and improved patient outcomes, TEG testing is emerging as an efficient method for the rapid diagnosis of post-traumatic coagulopathy. It is widely used in the operating room to direct transfusion protocols and many authors feel that it may have a similar role in the trauma setting.[35–37] Hyperfibrinolysis defined as a LY30 of 3% is an independent predictor of mortality (odds ratio 6.2, 95% CI 2.47 to 16.27) in severely injured pediatric trauma patients.[16] This increase in mortality with LY30 threshold of 3% is consistent with similar studies of adult trauma patients.[38, 39] This same pediatric trauma study also found hyperfibrinolysis occurred more frequently in

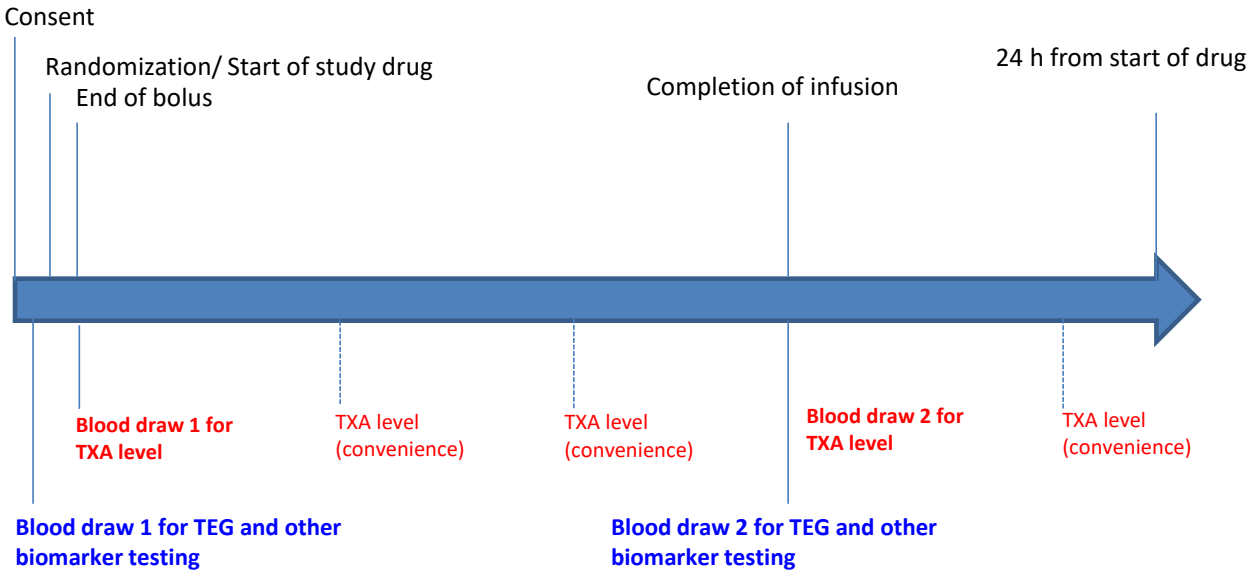


Figure 2: Flow diagram of blood draws for biomarker testing and TXA levels

children than similarly injured adults (24% vs. 9%).[16] Other studies have suggested different thresholds for defining hyperfibrinolysis[40] or other diagnostic measures such as rotational thromboelastography[41] or plasmin-antiplasmin complex levels.[42, 43] However these diagnostic measures are limited by their availability in the US[44] and their lack of real time results.[43, 45] Given the ability for TEG testing to provide clinicians quickly with data on fibrinolysis after trauma, TEG has been suggested as a means to directing antifibrinolytic therapy.[12, 39, 46]

The objective of obtaining TEG testing (see TEG parameters in Figure 3) for the pilot study is to demonstrate the feasibility of collecting TEG as part of study procedures. Potential issues such as timing of blood collection and blood processing have not been evaluated in a multicenter pediatric trauma trial. We will not analyze the association with TEG results and outcomes in the pilot study due to the small number of subjects enrolled, however we anticipate this analysis for the subsequent phase II/III trial.

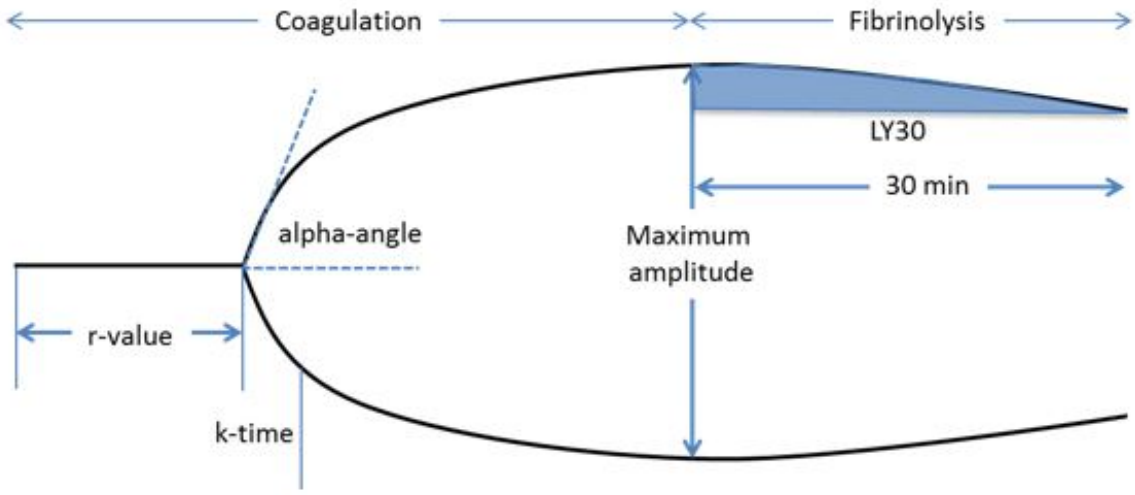


Figure 3: TEG parameters

Other biomarkers In addition to TEG, we will also measure other biomarkers that directly or indirectly measure fibrinolysis. Examples of these plasma biomarkers include: plasmin and d-dimer levels.

3.4 Data Collection During Hospitalization

Data collection during the ED stay and hospitalization is summarized in the Schedule of Evaluations (Figure 4 on page 23). After the initiation of treatment and recording of

baseline clinical and biochemical data, protocol procedures and ongoing data collection will continue for 7 days or until hospital discharge (whichever comes first).

3.4.1 TXA levels

We will collect blood samples at the end of the study drug bolus and again at the end of the study drug infusion to measure TXA levels (Figure 2 on page 20). In addition to these two blood samples, we will collect blood samples from routine blood draws during the first 24 hours after the start of study drug administration to measure serum TXA concentrations. In addition to these two blood samples, we will also collect blood samples during routine blood draws during the first 24 hours after ED arrival. The results from the TXA level measurements will be used for research purposes only and not be available to clinicians.

3.4.2 GCS score assessment and pupillary examination

GCS score assessment and pupillary exam will be collected at baseline. No repeat physical examination testing will be mandated during the study. We will collect GCS score assessment and pupillary examination results at 24 hours and at Day 7 or hospital discharge (whichever comes first) if completed as part of standard of care.

3.4.3 Blood product transfusion volume

Blood product transfusion volume will be measured at 24 hours, 48 hours, and 7 days or hospital discharge (whichever comes first) after randomization. This will include volume of PRBCs, platelets, plasma, and cryoprecipitate.

3.4.4 Hospital discharge information

Information will be collected after hospital discharge. Examples of data elements collected are:

- Hospital discharge date and time
- Destination upon discharge from hospital
- Abbreviated Injury Severity
- Mortality

Evaluation	Baseline	8h (end of gtt)	24h	48h	Day 7 or discharge (whichever first)	1 month	3 months	6 months
Screening and eligibility	X							
Consent and randomization	X							
Demographics/baseline information	X							
GCS score and pupillary exam	X		X (if done)		X (if done)			
Cranial CT scan (TBI patients)	X		X					
Routine laboratory tests (Hb, INR, pH, bicarbonate, Cr) (if done)	X							
Thromboelastography (TEG) and other biomarkers	X	X						
TXA level (collected at the end of bolus and infusion; also collect convenience sample of blood drawn during the first 24 hours after the start of study drug infusion)	X (end of bolus)	X	X (if done)					
Adherence assessment (time ICP is over 20 mmHg over the first 48 hours)				X				
Measurement of blood product transfusion			X	X	X			
Hospital disposition information					X			
Adverse events	X (randomization through discharge)							
Serious adverse events	X (randomization through discharge)							
PedsQL(All patients)					X (1 week)	X	X	X
GOS-E Peds (All patients)					X (1 week)	X	X	X
Digit span recall test (All patients 3 years and older)					X (1 week)	X	X	X
End of study								X

Figure 4: Schedule of Evaluations

3.5 Follow Up Data Collection

3.5.1 Pediatric Quality of Life (PedsQL), Pediatric GOS-E, and digit span evaluations

We will evaluate PedQL, Pediatric GOS-E, and the digit span recall test at Day 7, 1 month, 3 months, and 6 months post randomization. Subjects will be contacted via telephone by central assessor for these assessments. Below are the allowed windows for follow-up calls:

- 7 days = +7 day window
- 1 month = +14 day window
- 3 months = +4 week window
- 6 months = +4 week window

3.6 General Management Principles

To best discern the efficacy of TXA in the subsequent trial, it will be important to limit the variability of management of injured children. Heterogeneity of care such as differing transfusion practices or use of intracranial pressure monitoring devices may confound any potential efficacy or harm of TXA. However efforts to standardize general management principles must be balanced with the overall lack of definitive evidence on pediatric transfusion practices and TBI management. Each site will have an emergency physician, a trauma surgeon, a pediatric neurosurgeon, and a blood transfusion medicine physician included as co-investigators to assist in overseeing general management principles for this trial.

4 Study Procedures

4.1 Randomization (Enrollment)

Due to the narrow time window of study intervention, randomization must not delay treatment. To complete the randomization quickly, the study intervention will be preassigned using a central randomization process. Prior to enrollment at each site, a study drug box containing a vial of blinded study drug with a numeric identification code corresponding to the treatment assignment will be designated as the "Use Next Box."

"Use Next Box"

Because we will be evaluating TXA for different injury patterns (hemorrhagic torso injury, hemorrhagic brain injury, and hemorrhagic torso and brain injuries), randomization

will be stratified by injury type. Eligible subjects will be randomized into one of the three arms in a 1:1:1 ratio (TXA dose A, TXA dose B, or placebo). We will perform block randomization across types of injuries (i.e., torso or, brain or both torso and brain). To ensure sufficient number of injury types, we will limit the enrollment of subjects meeting the inclusion criteria for isolated brain injury (i.e., GCS less than or equal to 13 with associated intracranial hemorrhage) to a total of 20 subjects (as it is anticipated these will be the most common eligible subjects evaluated at the participating sites). Randomization will occur when drug infusion starts.

4.2 Study Drug Administration

4.2.1 Rationale for Study Doses

Enrolled subjects will be randomized to one of three study arms: TXA dose A, TXA dose B, or placebo. A systematic review demonstrated substantial variability in TXA dosing for pediatric surgical subjects, ranging from initial loading doses from 2 to 100 mg/kg IV, and a continuous infusion ranging from 3 to 10 mg/kg/hr.[30] Doses selected for this study and rationale are as follows:

- TXA dose A arm: Subjects will receive a 15 mg/kg bolus of TXA over 20 minutes followed by a 2mg/kg/hr infusion over 8 hours. The maximum bolus dose is 1000 mg, the maximum rate of infusion is 50 mg/min, and the maximum total maintenance dose is 1000 mg. This represents 31mg/kg total dose of TXA. This dosage is based on the dose studied in the CRASH-2 trial and has been recommended by a prior evidence statement (see Royal College of Paediatrics).[?] This dose is estimated to inhibit approximately 80% of fibrinolysis based on prior studies (Figure 5 on the facing page).[47]

- TXA dose B arm: Subjects will receive a 30 mg/kg bolus of TXA over 20 minutes followed by a 4 mg/kg/hr infusion over 8 hours. The maximum bolus dose is 2000 mg, the maximum rate of infusion is 100 mg/min, and the maximum total maintenance dose is 2000 mg. This represents 62 mg/kg total dose of TXA. This dosage represents approximately the 75th percentile dosage for children receiving TXA for non-traumatic surgical procedures in the PHIS database[48] and is estimated to inhibit 100% of fibrinolysis.[47] This dose is within the range recommended by the WHO[49] and has not demonstrated an increase in adverse events.[30]

- Placebo arm: Subjects in the placebo group will receive a bolus dose of normal saline over 20 minutes followed by a normal saline infusion over 8 hours (in the same weight-based volume as the other study arms).

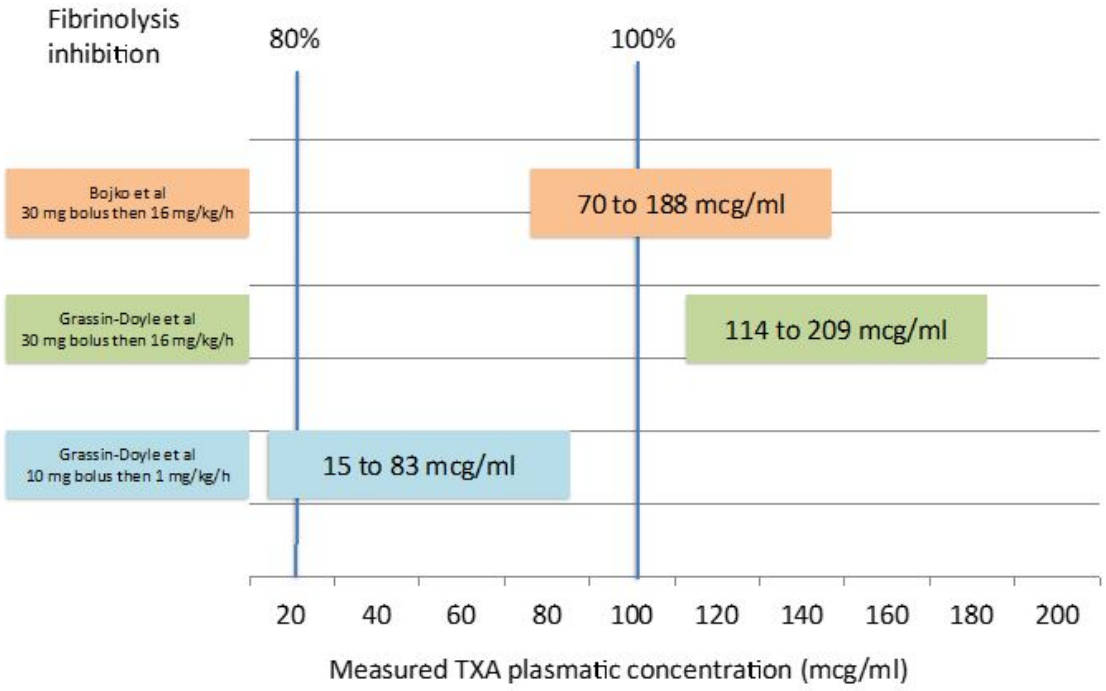


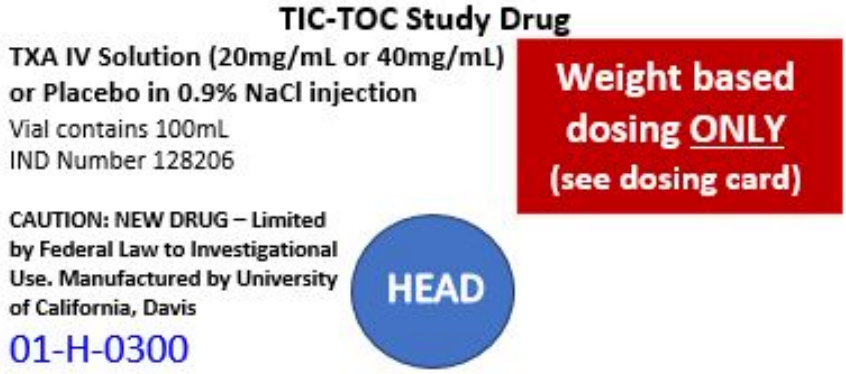
Figure 5: Plasma concentrations of TXA by dosing (Adapted from Koster et al.[47]).

In Figure 5, colored bars represent two different drug concentrations of IV bolus and infusion dosing from two prior studies (Bojko et al[50] and Grassin-Delyle et al[51]) and the subsequent measured TXA plasma concentration. A TXA plasma concentration of 20 mcg/ml inhibits approximately 80% of fibrinolysis and a concentration of 100 mcg/ml inhibits 100% of fibrinolysis.[52]

The UC Davis Good Manufacturing Practice Laboratory (Sacramento, CA) will prepare, package and store the investigational drug products (2 TXA arms) and the placebo arm at 2-8 °C. Both TXA infusions and the placebo infusion will be identical in color, volume, and packaging. The study drugs will be packaged in 100 ml glass infusion vials and will be clear and colorless. The concentration of TXA dose A will be 20 mg/ml of TXA in normal saline, TXA dose B will be 40 mg/ml of TXA in normal saline, and placebo will be 100 ml of normal saline. Each drug vial will have: 1) a numeric identification code that corresponds to the treatment assignment, 2) a label reminding clinical staff and study team members that weight-based dosing will be used, 3) a colored sticker identifying study vial by stratification, and 4) a hanger loop that can be peeled off to create a hanger.

4.2.2 Manufacturing and Distribution of the Study Drug

The study kits will be shipped to the clinical sites from the UC Davis GMP facility at 2-8 °C. Shipping will be conducted under controlled conditions under a chain of custody documentation and a data log included in shipment. The product will be stored by the IDS Pharmacies at the sites at 2-8 °C until dispensed. The IDS Pharmacies will store at least 1 study vial for each study arm. The number of vials stored at each IDS Pharmacy may be modified depending on the rate of enrollment for each site.



Example of study label

After enrollment, the study vial numeric identification code will be entered into an

online data management system by the study team. The study team will obtain a backup study vial from the IDS Pharmacy, corresponding to the recently used study vial (e.g., torso study vial will replace torso study vial). The backup study vial will then be placed in the corresponding Use Next Box that will be stored in a secure automated medication dispensing system in the ED. There will be Use Next Boxes for each study arm in the ED. Each Use Next Box will contain a corresponding study vial and a weight-based dosing chart described below.

All individuals providing clinical care at the study sites (physicians, nurses, laboratory technicians, respiratory therapists, pharmacists, etc.) and the study team (research coordinators, research assistants, and site investigators) will be blinded to allocation and dosing, as will the subjects.

4.2.3 Study Drug Administration

The study box will be stored in a secure automated medication dispensing system in the ED at temperatures 2-8 °C. When a subject is ready to be enrolled into the study (Figure 8 on page 33), a member of the clinical staff will remove the "Use Next Box" from the secure automated medication dispensing machine in the ED and follow the weight-based dosing chart provided in the box. An infusion pump will be programmed with the determined rate and volume of the bolus and maintenance dose. All doses of study drug will be administered intravenously. An initial bolus dose will be given to the subject over 20 minutes, immediately followed by the maintenance infusion over 8 hours. Rates are provided on the dosing chart. Each 100 ml vial of study drug will have sufficient volume of study drug for both the bolus and infusion doses. After enrollment, the study team will load the study site's back-up vial into the "Use Next Box". There will be three "Use Next Boxes" one for torso injuries, one for brain injuries and one for both torso and brain injuries, each with a corresponding study vial.

For children weighing less than 35 kg, a syringe pump with a volume of 60 ml will typically be used. If a syringe pump is used, the total volume for both the bolus and maintenance infusion will be withdrawn (plus an additional 2 ml to account for priming of the syringe pump tubing) from the 100 ml study vial and loaded into the syringe pump. The infusion line will be primed with study drug (typically 2 ml) prior to infusion. At the end of the maintenance infusion, the syringe pump tubing will be disconnected and discarded. The infusion line will not be flushed.

For children weighing 35 kg or more, it is recommended that the 100 ml study vial will be directly spiked with a standard vented IV administration set. The vial will be inverted and hung from the attached plastic loop. The infusion line will be primed with study drug (typically 10-14 ml). At the end of the maintenance infusion, there may be

remaining study drug within the infusion line. A sufficient amount of sterile 0.9% sodium chloride may be used to ensure that all remaining study drug is infused from the line and administered to the subject.

The study arms will be blinded. Therefore, the same weight-based volume will be infused for each arm. The volume for the infusion will be determined by the estimated or calculated weight of the child. The weight-based dosing for all arms are described in Figure 6 on the facing page.

The weight-based dosing in Figure 6 on the next page corresponds to the total doses of TXA dose A and TXA dose B displayed in Figure 7 on page 32.

For children with moderate renal impairment(estimated glomerular filtration rates 30-59 mL/min/1.732 [as calculated by the bedside Schwartz method]) we will reduce the dose by 50%. This will be accomplished by reducing the rate of study drug administration by 50%. For example, if the child weighs more than 60 kg, the maintenance infusion rate should be 6.25 ml/hr over 8 hours. If moderate renal impairment is identified, the rate will be reduced to 3.125 ml/hr over 8 hours. This rate adjustment will occur as soon as moderate renal impairment is identified. If severe renal impairment is identified, the study drug will be discontinued.

4.2.4 Discontinuation of Study Drug

The study drug will be discontinued if any of the following occur:

- Suspected anaphylactic reaction
- Severe renal impairment (creatinine clearance less than 29 mL/min/1.73m2) is identified on baseline or subsequent laboratory measurements
- Withdrawal of consent by the subject's legal guardian or legally authorized representative
- Discovery of new information which makes the subject ineligible to continue participation in the study (e.g.,exclusion criteria such as pregnancy, prisoner, history of seizures or clotting disorders)

4.3 Blinding and Unblinding

Both subjects and study team members are blinded to the interventional arm. Blinding is provided by the use of identical study drugs, packaging, volume, and rate of infusion.

Unblinding is not allowed. Clinicians should assume that the subject has received TXA and treat accordingly.

Estimated weight in kg (calculated weight)	BOLUS volume (TXA Arm A, B, or placebo) (total ml)	BOLUS rate (ml/hr) over 20 min	MAINTE-NANCE volume (TXA Arm A, B, or placebo) (total ml)	MAINTE-NANCE rate (ml/hr) over 8 hours	Length based color on Broselow tape
3-4.9	3	9	3	0.375	Grey
5-7.4	5	15	5	0.625	Pink
7.5-9.9	7	21	7	0.875	Red
10-12.4	9	27	9	1.125	Purple
12.5-14.9	11	33	11	1.375	Yellow
15-19.9	14	42	14	1.75	White
20-24.9	18	54	18	2.25	Blue
25-29.9	22	66	22	2.75	Orange
30-34.9	26	78	26	3.25	Green
35-39.9	30	90	30	3.75	
40-49.9	36	108	36	4.5	
50-59.9	44	132	44	5.5	
>60	50	150	50	6.25	

Figure 6: Weight-Based Dosing for All Arms

Estimated Weight in kg (calculated weight)	BOLUS Total Dose (mg) TXA dose A: 15 mg/kg bolus over 20 min then 2 mg/kg/hr over 8 hrs Concentration: **20** mg/ml in a 100 ml vial	MAINTENANCE Total Dose (mg) TXA dose A: 15 mg/kg bolus over 20 min then 2 mg/kg/hr over 8 hrs Concentration: **20** mg/ml in a 100 ml vial	BOLUS Total Dose (mg) TXA dose B: 30 mg/kg bolus over 20 min then 4 mg/kg/hr over 8 hrs Concentration: **40** mg/ml in a 100 ml vial	MAINTENANCE Total Dose (mg) TXA dose B: 30 mg/kg bolus over 20 min then 4 mg/kg/hr over 8 hrs Concentration: **40** mg/ml in a 100 ml vial
3-4.9	60	60	120	120
5-7.4	100	100	200	200
7.5-9.9	140	140	280	280
10-12.4	180	180	360	360
12.5-14.9	220	220	420	420
15-19.9	280	280	560	560
20-24.9	360	360	720	720
25-29.9	440	440	880	880
30-34.9	520	520	1040	1040
35-39.9	600	600	1200	1200
40-49.9	720	720	1440	1440
50-59.9	880	880	1760	1760
>60	1000	1000	2000	2000

Figure 7: Weight-Based Dosing of TXA Dose A and TXA Dose B

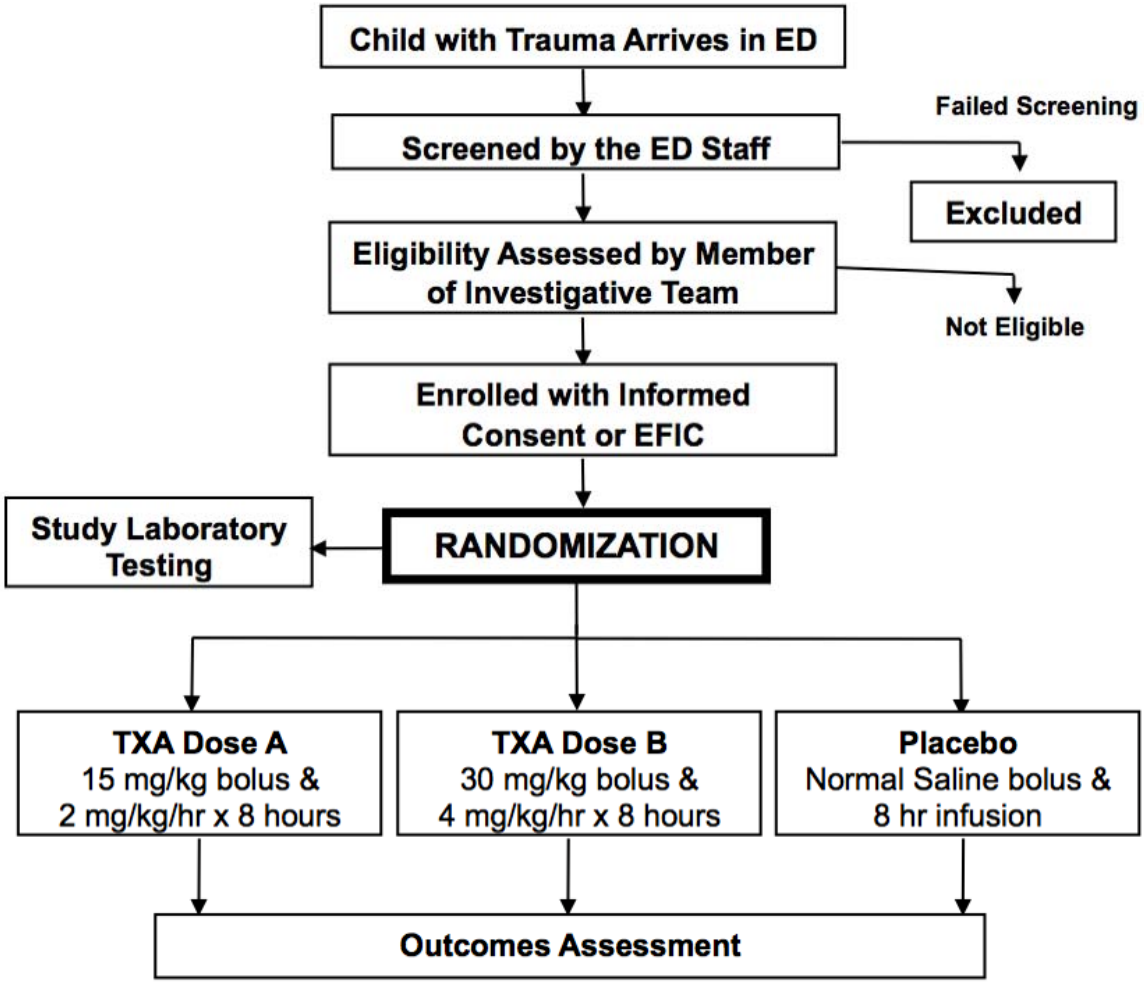


Figure 8: Study Flow Chart

5 Data Analysis

5.1 Outcomes

As this study is a pilot trial to collect preliminary data on safety and efficacy and to assess feasibility of study procedures, the study is not powered for a particular endpoint. We will collect the following outcomes: total blood products (ml/kg) transfused over the initial 48 hours of care (children with torso injury), and intracranial hemorrhage progression in first 24 hours (children with TBIs). We will also measure PedsQL^{TM} (Pediatric Quality of Life Inventory), Peds GOS-E, and digit span recall at 1 week, 1 month, 3 months, and 6 months post-randomization (all subjects) Figure 9.

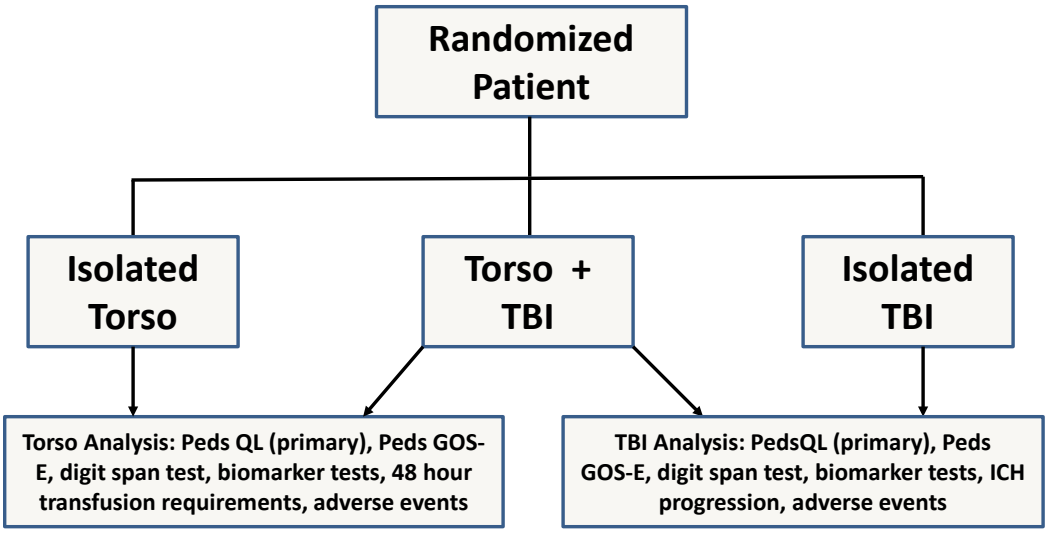


Figure 9: Outcome Determination

5.1.1 Blood Transfusion

Blood product transfusion will be calculated as the total mL/kg from randomization to 48 hours after randomization. Blood products used in the calculation will include packed red blood cells (PRBC), platelets, fresh frozen plasma (FFP), and cryoprecipitate.

Rationale: Management of children with significant traumatic hemorrhage involves both the cessation of active bleeding and administration of blood products to correct for hemorrhage-induced anemia and coagulopathy. Most of the initial and ongoing hemorrhage occurs in the first 48 hours after injury.[53] While patients with substantial blood loss and/or trauma-induced coagulopathy can benefit from blood product transfusion, it is not without substantial risk. Transfusion of PRBCs after trauma is independently associated with increased risk of death and adverse events.[54, 55] Transfusion of blood products is associated with the transmission of infectious diseases, immune sensitization, post-operative infectious complications, transfusion related acute lung injury (TRALI), renal dysfunction, multiple organ failure, increased intensive care unit and hospital length of stay, and increased short- and long-term mortality.[56, 57] Surgical data suggests that with each unit of PRBC transfused, the risk for an adverse outcome is incrementally increased. It is estimated that 0.5 to 3% of all transfusions result in some adverse event.[57]

Transfusion of blood products is also costly. Based on a study published in 2006, the cost of transfusing a single unit of PRBCs is between 1,600 US dollars and 2,400.[58] US dollars. Blood transfusion costs are also steadily increasing and will continue to increase over time as additional blood product safety and screening measures are implemented.[59] Additionally, blood transfusion related adverse events account for increased costs, largely the result of increased hospital length of stay.[59]

Prior to the start of the study, the collaborating trauma surgeons and collaborating transfusion medicine physicians (1 from each site), as well as other collaborators including EM and ICU physicians, will establish general guidelines for indications for blood product transfusion.

5.1.2 Intracranial Hemorrhage Progression at 24 hours (plus or minus 6 hours)

We will measure intracranial hemorrhage progression at 24 hours in all subjects with intracranial hemorrhage on the initial clinical CT scan (excluding those who received a neurosurgical intervention). We will perform a second non-contrast head CT scan 24 (plus or minus 6) hours after randomization, for research, to assess intracranial hemorrhage progression (for those who have not received a second head CT scan in the specified time frame in the course of clinical care). Additional brain-imaging studies may be performed at the discretion of the treating physician as a part of routine care. A central

radiologist, blinded to clinical data, will review cranial CT scans and calculate intracranial hemorrhage progression using the ABC/2 volume estimation.[60] Intracranial hemorrhage will be assessed relative to the total brain volume (calculated by the XYZ/2 volume estimation).[61, 62]

Rationale: Most intracranial hemorrhage progression occurs in the first 24 hours of injury.[63, 64] Intracranial hemorrhage size is strongly associated with functional outcomes.[65] Given that TXA attenuates hemorrhage, intracranial hemorrhage progression is an important outcome measure for subjects with TBIs.[65]

5.1.3 PedsQL

We will assess neurocognitive functioning and other quality-of-life measures using the Pediatric Quality of Life Inventory (PedsQL) at 1 week, 1 month, 3 months, and 6 months for all enrolled children.

Rationale: The PedsQL measures health-related quality of life in healthy children and adolescents as well as those with acute and chronic health conditions.[66] The PedsQL generic core scales are comprised of 23 questions that measure the core dimensions of health as delineated by the World Health Organization. The four multidimensional scales include: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). These four scales produce three summary scores: total scale score (23 items), physical health score (8 items), and psychosocial health score (15 items). The PedsQL is practical (less than 4 minutes to complete), developmentally appropriate, reliable (excellent correlation between child self-report and parent proxy-report), valid (distinguishes between healthy children and children with acute and chronic health conditions), and has been translated into multiple languages. There are more than 850 publications reporting research that has used the PedsQL measure. For TBI, PedsQL is reliable in differentiating between moderate and severe TBI.[67] The PedsQL has been recommended by the Common Data Elements (CDE) TBI Outcomes Workgroup (in conjunction with NINDS) as a core quality-of-life measure post-TBI and a primary measure of global outcome.[68] The PedsQL is a continuous score that ranges from 0-100. A clinically meaningful difference has previously been shown to be 4.5 points on the PedsQL scale (minimum difference that subjects and their parents perceive to be important).[69] The PedsQL will be administered to subjects over the telephone.

5.1.4 Glasgow Outcome Score Extended (GOS-E) Peds

We will assess GOS-E Peds at 1 week, 1 month, 3 months, and 6 months for all enrolled children.

Rationale: The GOS-E Peds was developed as an age-appropriate, valid measurement of outcome necessary to complete randomized clinical trials in infants and children less than 17 years of age with TBI. The GOS-E Peds has been demonstrated discriminant validity for mild, moderate, and severe TBI and is associated with changes in TBI sequelae over time.[66] The GOS-E has been recommended as a core measure global outcome in TBI studies.[68] For this proposal, the PedsQL and GOS-E Peds assessments will be administered to all enrolled subjects over the telephone.

5.1.5 Digit Span Recall Test (working memory)

We will assess working memory using the digit span recall test at 1 week, 1 month, 3 months, and 6 months for all enrolled children 3 years and older.

Rationale: The digit span recall test evaluates working memory.[70–72] Participants are asked to repeat a series of numbers heard aloud, in the same order as spoken (forward digit span), and then are asked to do the same backwards. The forward task measures the ability to maintain information in line, whereas the backward task measures the ability to mentally manipulate information.[73] The examiner increases the numbers of digits by one unit on each successive trial as long as the child repeats them correctly. The test ends when the child makes a mistake in two sequences in the same span in a row.

5.1.6 Biomarkers

For each candidate biomarker, we will compute the within-person time 1 to time 2 change score and then estimate between-group (high-dose vs. low-dose TXA) differences in mean changes, along with 95% confidence intervals.

5.1.7 Safety Outcomes

Safety outcomes will be assessed at Day 7 or at hospital discharge (whichever comes first) via review of the electronic medical record and include:

- Thromboembolic disease: any venous or arterial thrombosis on standard diagnostic imaging post-randomization (including deep vein thrombosis, pulmonary embolism, sinus thrombosis, myocardial infraction, ischemic stroke)

- Seizures occurring within the initial 24 hours of drug: clinical or electroencephalogram-documented (seizures are a possible side effect of TXA)

5.2 Randomization and Stratification

Subjects will be randomized into one of three arms (TXA dose A, TXA dose B, or placebo). Subjects will undergo block randomization to ensure equal distribution of types of injuries across the three arms Figure 10. To ensure sufficient number of injury types, we will limit the enrollment of subjects meeting the inclusion criteria of GCS score less than or equal to 13 with intracranial hemorrhage (Isolated TBI) to a total of 20 subjects (as these are the most common subjects evaluated at the participating sites).

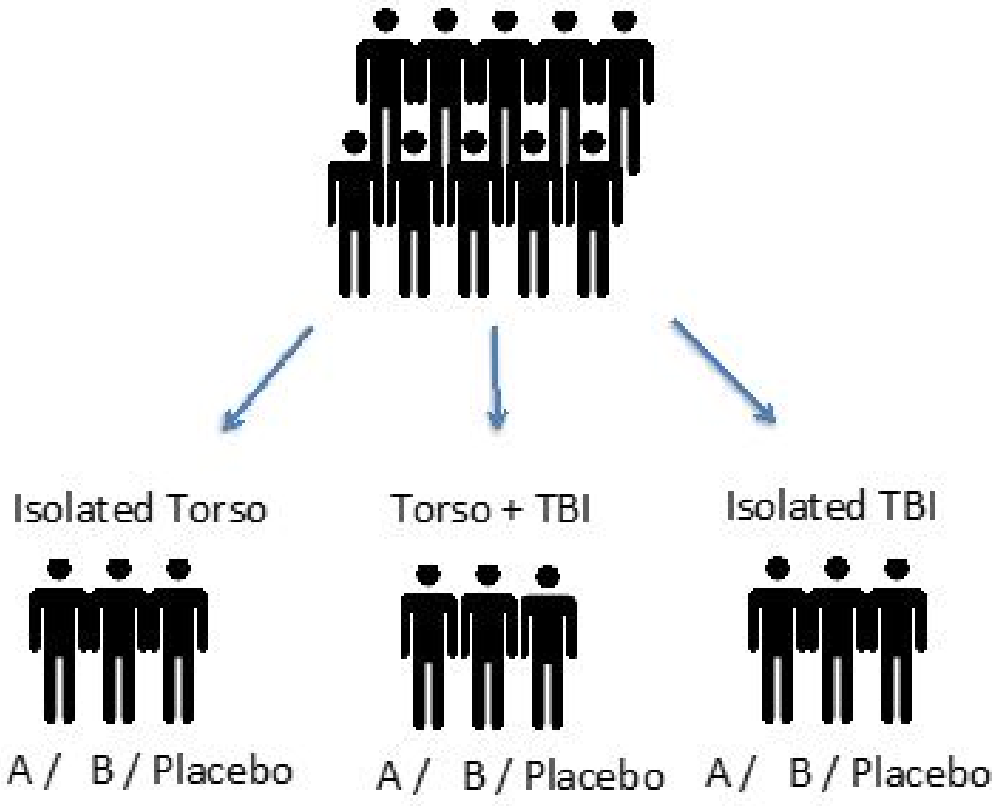


Figure 10: Block Randomization

6 Data Management

6.1 Clinical Site Data Management

The Data Coordinating Center will create the electronic data capture (EDC) system and worksheets that can be used by clinical site research coordinators and investigators. Data will be entered via the Web into the EDC. Worksheets and study documents will be maintained in locked filing cabinets in locked offices at each site.

6.2 Electronic Data Capture System

The Data Coordinating Center currently uses OpenClinica, REDCap, and XNAT as its data capture systems; this may be changed at any time without requiring a protocol amendment.

6.3 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous PECARN studies, and we will utilize this process to ensure excellent quality data in the proposed study. Our site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Site monitors must be provided with full access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

6.3.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found. Remote site monitoring schedules will be determined by the Data Coordinating Center in coordination with the study principal investigators.

6.3.2 Clinical Site Monitoring

Site monitoring visits will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close out visit. The site initiation may take place as group training made up of site investigators and research assistants.

6.3.3 Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record, subject study file, regulatory documentation, or other source documents to the Data Coordinating Center staff, who review those materials against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring the documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

6.3.4 Pharmacy Monitoring

The Clinical Center pharmacy must maintain adequate records of all dispensed study drug. Each pharmacy will be monitored and may be requested to send copies of these documents to the Data Coordinating Center. Since this study will use a central pharmacy, that pharmacy must also maintain adequate records and will also be monitored.

6.4 Data Coordinating Center

6.4.1 Data Center Description

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a

variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1400 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 99% of its environment. The virtual environment consists of more than 200 virtual servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware of software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture is no longer be a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,

- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. DCC storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

DCC information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

6.4.2 Security and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2012 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using transport layer security (TLS) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the TLS protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2012 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

6.5 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders, and the Institutional Review Board (IRB) for each study site.

7 Protection of Human Subjects

7.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center and each clinical center must obtain approval from their respective IRB prior to participating in the study. A central IRB (cIRB) at the University of Utah will be used for this clinical trial.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

7.1.1 Reporting of IRB Actions

Protocol Amendments Changes in the protocol which have been approved by the Central IRB will be submitted upon IRB approval to the FDA, as required under 21 CFR 312.30(b), and NHLBI prior to implementation. Upon notice that the protocol amendment has been received at the FDA and NHLBI, the protocol amendment will be distributed to sites. Sites will be instructed that they must follow local policies in implementing the protocol amendment including obtaining local IRB approval, if required.

7.2 Informed Consent

We will enroll eligible patients who are younger than 18 years of age. Because eligible patients are severely injured and will frequently arrive to the emergency department (ED) without their parents or guardians, we will have a multifaceted approach to consent (Figure 11 on the next page). We will attempt to obtain written informed consent at the time of patient eligibility if the parent or guardian is available and able to provide informed consent. However, because the therapeutic window of TXA is narrow, and the parent or guardian will frequently be unavailable or unable to provide consent (e.g., severely injured or emotionally incapacitated) at the time that the patient is determined to be eligible, we will also use federal Exception from Informed Consent (EFIC) procedures as described below.

Parental Permission (when present and reasonable time to obtain informed consent)

After determining that a subject is eligible, and the parent or guardian is present in the ED and able to provide informed consent, the site investigator or designee will approach the parent or guardian to offer participation for their child in the study (Figure 12 on page 46). The parent or guardian will be informed about the objectives of the study, the study procedures, and the potential risks and benefits of participation. If the parent or guardian refuses permission for their child to participate, then all clinical management will be provided by the clinical staff in accordance with institutional practice and judgment.

We will seek written documentation of parental permission from the subject's parent or guardian as soon as possible. Under FDA Regulation 21 CFR 50.55(e)(1), where clinical investigations are more than minimal risk but presenting the prospect of direct

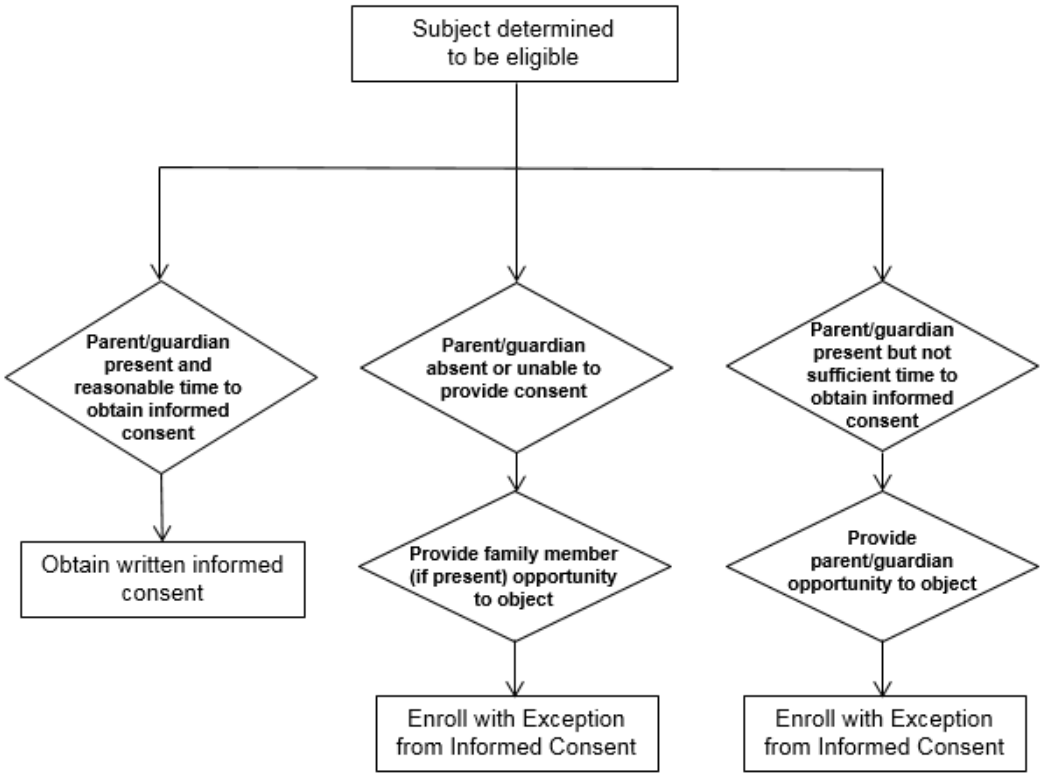


Figure 11: Informed Consent Procedures

benefit to individual subjects (50.52) and permission is to be obtained from guardians, permission of one guardian is sufficient.

Under FDA Regulation 21 CFR 50.55(c)(2), because the intervention holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of the clinical investigation, assent of the child is not a necessary condition for enrollment in the study.

Subject Consent

Subjects who are eligible for this study must be younger than 18 years of age at the time of enrollment. If a subject reaches the age of 18 years after enrollment but during the study period, then informed consent of the patient becomes applicable. If this occurs, 18 year-old subjects who are alert and competent and capable of giving consent will be asked, following an appropriate discussion of risks and benefits, to give consent to the

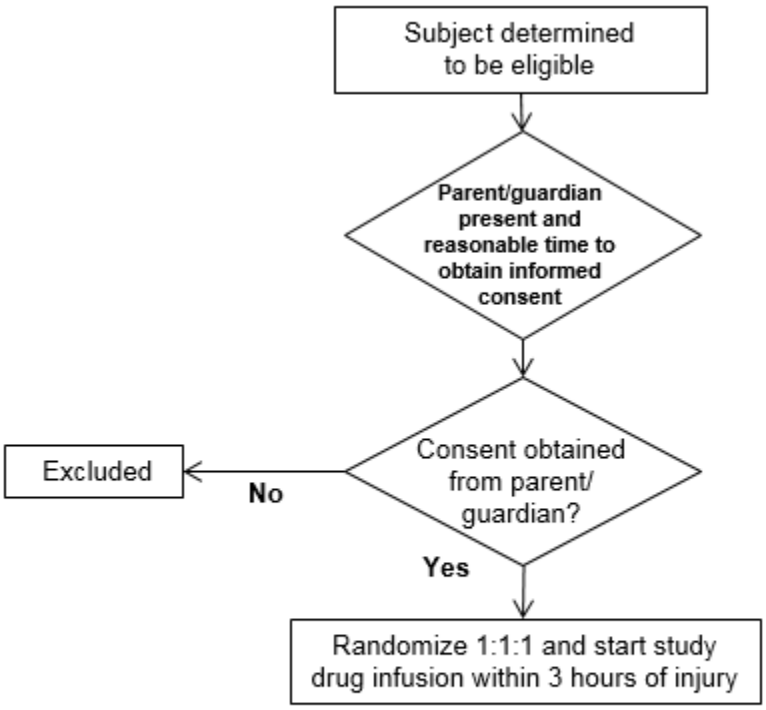


Figure 12: Parent/guardian present and reasonable time to obtain informed consent

study for further study procedures. We will obtain informed consent from these subjects for continuation in the study. Continued participation will consist of a telephone follow up call, considered to be minimal risk. Subject consent will be waived if the subject has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board.

7.3 Exception from Informed Consent (EFIC)

We will use EFIC procedures when the parent or guardian is not present or unable to provide written informed consent. See Section 7.3 for justification of EFIC procedures.

EFIC when the parent/guardian is not present or is unable to provide written informed consent

We will enroll patients using EFIC procedures if the parent or guardian is not present or is unable to provide written informed consent (e.g., parent is also severely injured or is emotionally incapacitated) at the time eligibility is determined (Figure 13 on the next page).

If the parent or guardian is not present at the time eligibility is confirmed or is unable to provide written informed consent, a family member who is present will be provided the opportunity to object to the enrollment. In this scenario, the family member(s) will be provided a brief overview of the study and an explanation on why we are unable to obtain written informed consent due to the absence of the parent/guardian and the narrow therapeutic time window. If the family member present objects to the patient's enrollment into the study, the patient will not be enrolled under EFIC procedures. If no objections are made to the patient's enrollment into the study, the patient will be enrolled using EFIC procedures.

EFIC when the parent/guardian is present but there is not sufficient time to obtain informed consent

We will enroll patients using EFIC procedures if the parent or guardian is present and there is not sufficient time, at the time eligibility is confirmed, to obtain written informed consent and complete randomization. The parent and the guardian, however, will be provided the opportunity to decline enrollment (Figure 14 on page 49).

In this scenario, the parent or guardian will be provided a brief overview of the study and an explanation on why we are unable to obtain written informed consent due to the narrow therapeutic time window. If the parent or legal guardian objects to the patient's enrollment into the study, the patient will not be enrolled under EFIC procedures. If the parent or guardian agrees to the patient's enrollment into the study, the patient will be enrolled using EFIC procedures.

Obtaining informed consent after the use of EFIC

The use of EFIC does not obviate the need for parent or guardian consent. If EFIC procedures are used, once the patient has been randomized and administration of study drug has been initiated, the investigative team will attempt to obtain written informed consent from the parent or guardian.

The parent or guardian will be informed of the patient's inclusion into the study and informed of the benefits and risks of the study. At that time, the parent or guardian

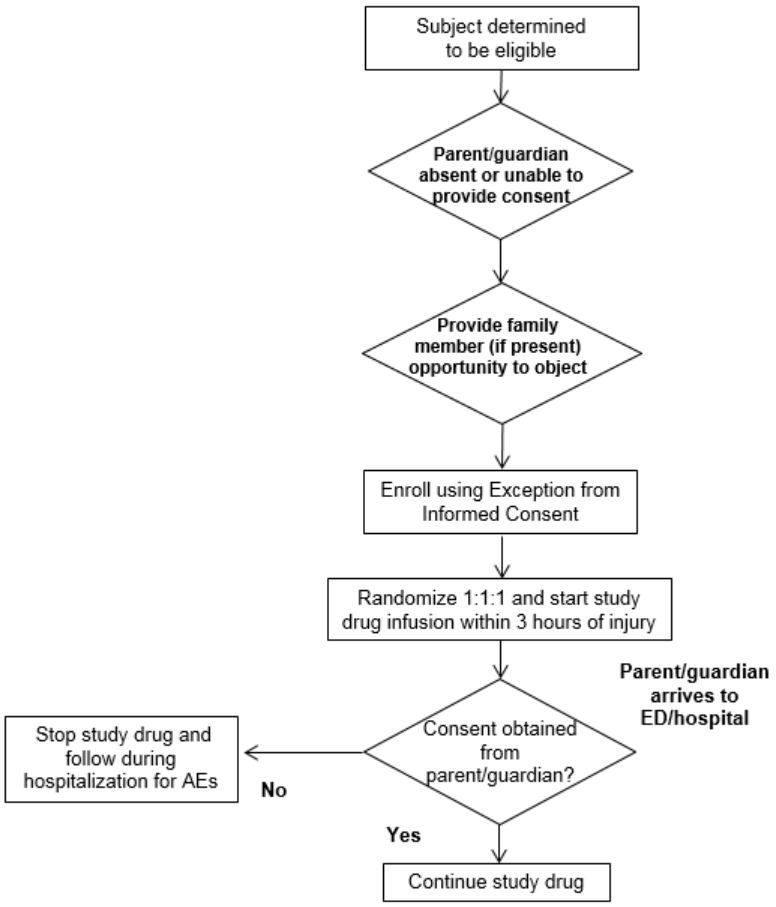


Figure 13: Parent/guardian absent or unable to provide informed consent

will be given the option of allowing the patient to continue in the study, or to cease the subjects participation. If the parent or guardian requests that participation be stopped during study drug infusion, the study drug will be stopped immediately, although the parent or guardian will be asked if the patient could continue to be followed and evaluated through the 6-month time point. If the parent or guardian agrees to allow the patients continued participation or desires stopping the study drug, but will allow follow-up, an appropriate written informed consent form will be signed by the parent or guardian.

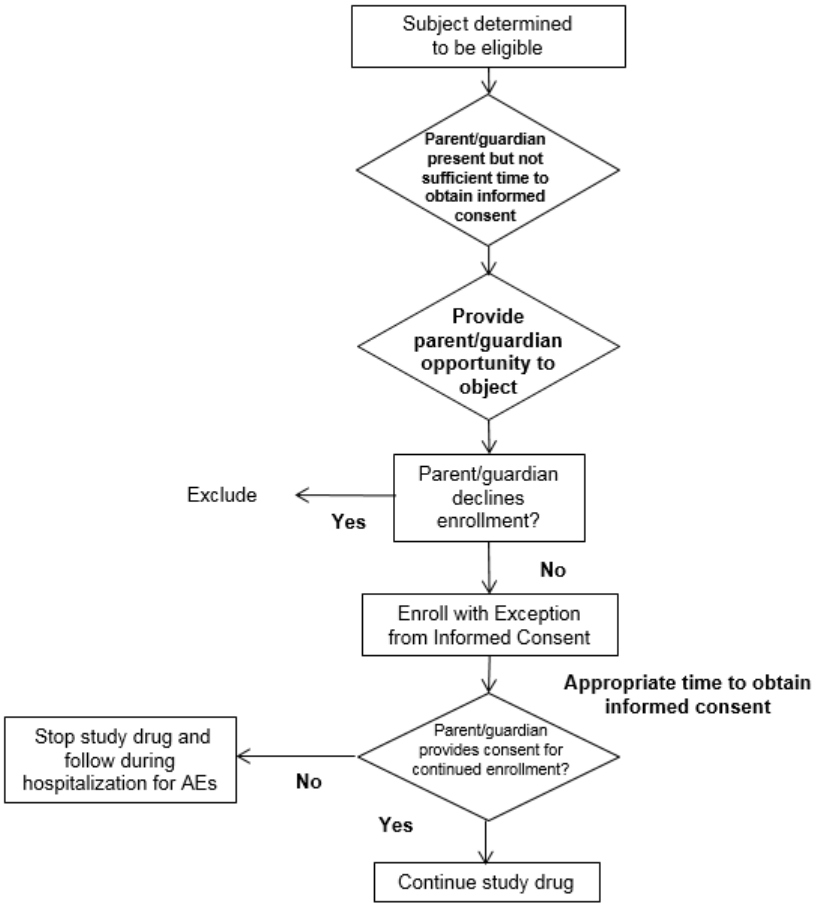


Figure 14: Parent/guardian present but not sufficient time to obtain informed consent

Justification for EFIC

This research meets the criteria for EFIC specified in FDA Regulation 21 CFR 50.24 for the following reasons:

- *The human subjects are in a life-threatening situation that necessitates urgent intervention;*

  Enrolled children will have significant hemorrhagic injuries that are life-threatening.

- *Available treatments are unproven or unsatisfactory;*

  Currently, no therapy is available to stop hemorrhage beyond surgical cessation. No intravenous medications are available to assist in the cessation of hemorrhage.

Thus, TXA has the potential to be the first therapeutic medication in children with hemorrhagic injuries.

- *Collection of valid scientific evidence is necessary to determine the safety and efficacy of the intervention;*

  Scientific evaluation through a randomized clinical trial is necessary to further test the efficacy and safety of the proposed intervention.

- *Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition;*

  Parents are frequently absent because either their children arrive in ambulances without them or the parents are victims of the traumatic events that involve the patients.

- *The intervention must be administered before consent can be obtained from the subjects parent/ guardian;*

  Obtaining informed consent from the patients parent/guardian is not feasible due to the narrow therapeutic window of TXA. The greatest benefit of TXA for adults with hemorrhagic trauma is within one hour from the time of injury, and the total therapeutic window is only up to 3 hours after injury. After 3 hours, there is suggestion of harm from TXA infusion based on a large adult randomized control trial of injured adults (Figure 15 on page 52).[20]

  We have previously shown that 45% of children with head trauma present to the ED without their parent or guardians.[74] More importantly, more severely injured children are more likely to present without a parent or guardian. Sixty-six percent of children with GCS scores of 3 to 13 presented without a parent or guardian while in children with GCS scores ≤ 8, none had a parent or guardian present at the time of ED presentation.[74] Our second study on the topic demonstrated across multiple centers that among children with GCS scores of 3 to 12 following injury, the parent or guardians for one-half of the patients do not present to the ED within the initial 3 hours of their child's care.[75]

  From a safety perspective, in the CRASH-2 trial evaluating TXA in adults with hemorrhagic trauma, hospitals that waived the requirement for informed consent started treatment 1.2 hours earlier (95% CI 0.7-1.8) compared to hospitals where written consent was required from relatives (Figure 16 on page 53).[76] Because the benefit of TXA is better the earlier it is administered, it was estimated that this 1.2 hour delay reduced the proportion of patients who would have benefitted from the drug by 14%. Moreover, from a feasibility perspective, if all the sites

required written informed consent for enrollment, the study would have likely been a negative trial. A separate trial of adults with TBI evaluating the use of progesterone, estimated the requirement for informed consent delayed enrollment by 4 hours based on hypothetical modeling.[77]

- *There is no reasonable way to identify prospectively individuals likely to become eligible for participation;*

  There is no reasonable way to prospectively identify potential patients because our patient population consists of trauma patients.

- *Participation in the research holds out the prospect of direct benefit to the subjects;*

  Pursuant to 21 CFR 50.24(a)(3): i) the proposed subjects are in life-threatening situations requiring intervention, ii) prior pediatric and adult clinical data have demonstrated clinical benefits of TXA use suggesting the potential for direct benefit to the proposed subjects, and iii) these data have demonstrated no increase in adverse events with the use of TXA, suggesting a reasonable risk-benefit tradeoff for this condition. Thus, the potential benefit of improved hemostasis, decreased blood product requirements, hemorrhage attenuation/mitigation, and improved functional outcomes substantially outweigh the risks, under FDA EFIC guidance.

- *The clinical investigation could not practicably be carried out without the waiver;*

  Enrolling only patients that have their parent or guardians present within the treatment window to consent would not be feasible and also create significant enrollment bias, thereby limiting the scientific validity of such a study design.

7.4 Waiver of Informed Consent

Waiver of consent is requested for observational data collection for each subject eligible for this study. The justification for waiver of consent for the observational data collection in this study is based on the following factors:

1. The scientific validity of the study is dependent on capturing all eligible subjects during the period of study, as one of the major goals is to accurately describe the characteristics of the entire eligible population.

2. This part of the study involves no intervention and collection of observational data will not require any subject or parent contact.

3. The minimal risk of loss of privacy is mitigated by secure data management at the DCC, and analysis datasets will be de-identified.

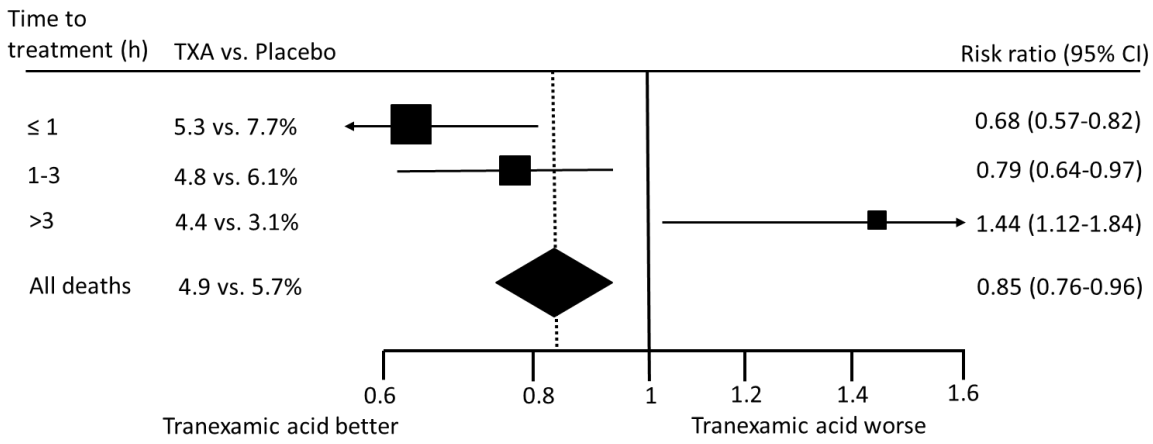


Figure 15: Mortality by time to treatment

7.5 Potential Risks

A systematic review of children undergoing non-traumatic surgery suggests no increased risk of complications following TXA treatment.[30] However, injured children were not included in that systematic review and the authors acknowledge that none of the trials included were powered to assess safety.[30] The CRASH-2 trial, a large trial of TXA in injured adults, also suggested no increased complications in the TXA group.[19] Thus, we do not anticipate an increased risk of complications in injured children receiving TXA compared to placebo. The study, however, will monitor for specific potential risks as described below.

The most important theoretical side effect of TXA is acute thrombosis, either arterial or venous.[78, 79] Acute thrombotic events are defined as vascular thrombosis resulting in any of the following: cardiac ischemia, cerebral thrombosis, bowel infarction, deep venous thrombosis, or pulmonary embolism. Seizures have been reported in cardiac surgery patients receiving very high doses of TXA (61 to 259 mg/kg) with most receiving greater than 100 mg/kg.[80–84] Although, the seizures were believed to be related to cerebral ischemia associated with the cardiopulmonary bypass rather than TXA,[80] others have suggested the seizures may be secondary to TXA inhibition of gamma-aminobutyric acid receptors in neurons.[81] Furthermore, the reported doses of TXA are substantially higher than planned in this study. In addition, seizures are a complication of severe trauma, especially in patients with traumatic brain injuries and those with episodes of hypoxia. Thus, we will evaluate for these potential complications but do not anticipate that seizure events are secondary to the doses of TXA planned for use in this study. Lastly, cerebral

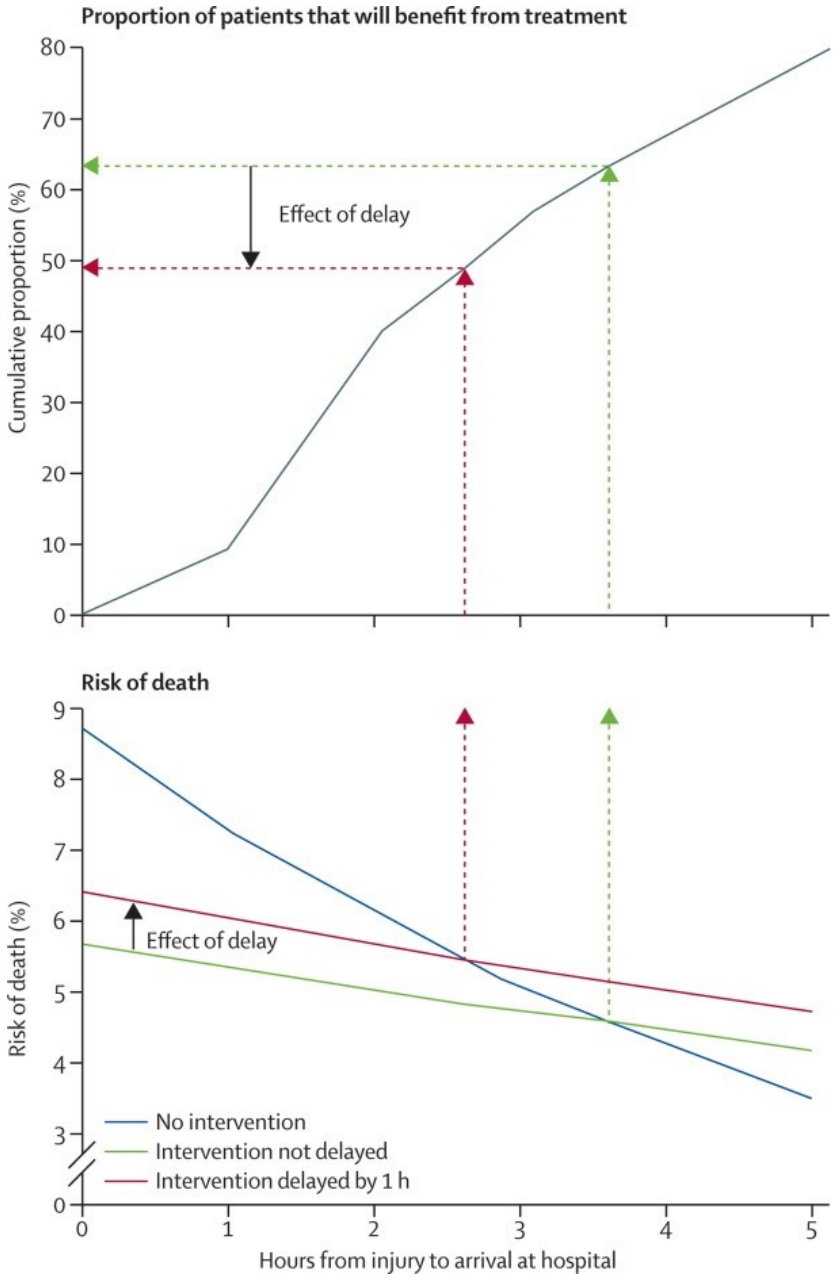


Figure 16: Effect of 1 hour delay in start of treatment with TXA on proportion of patients who will benefit and on risk of death

infarction may occur in patients with spontaneous subarachnoid hemorrhages.[78, 85] Thus, we will specifically assess for cases of cerebral infarction.

In addition to the above, subjects presenting with gross hematuria or renal injury who do not meet exclusion criteria may still be at risk for ureteral obstructions. Investigators should consider this possibility when enrolling subjects and should closely monitor urine output and evaluate for ureteral thrombosis/obstruction in subjects with renal/bladder injuries.

Other side effects of TXA that we will monitor include symptoms listed in the package insert such as gastrointestinal disorders (nausea, vomiting, and diarrhea) and allergic dermatitis. These may occur at rate of 1-10%.

In addition to TXA administration, there may be added discomfort to the participant with the additional blood collection. However, research samples will be collected at the same time as a standard of care samples whenever possible to minimize extra needle pokes to the participant. This research study may also involve one head CT scan for head injury patients. This scan is not standard of care and study participant would be receiving it only because they are enrolled in this research study. These procedures will expose the participant to radiation. The risk from this radiation exposure is considered to be small and comparable to other every day risks. To give an example of how much radiation the participant will receive, we will compare this radiation to the radiation that the participant receives from natural sources. Everyone receives a small amount of unavoidable radiation every day. Some of this radiation comes from space while some comes from radiation that is naturally occurring in water, soil, rocks and minerals found in plants and animals. The excess radiation that the participant will be exposed to in this research study is equivalent to about 9 months of natural background radiation. This amount does not include any radiation exposures that the participant may receive from other types of tests. Radiation exposure has the potential to lead to cancer later in life. The exact risk is not known, but the risk is believed to be 2-5 times higher in children than in adults exposed to the same radiation dose.

The risks to subjects in this proposal are reasonable in relation to the potential benefits of participation. The study risks will be minimized by very careful monitoring of neurological, hemodynamic, and renal function status of study participants.

7.6 Protections Against Potential Risks

Subjects enrolled in the study will be monitored carefully for the development of any potential complications as described above. Subjects will be evaluated frequently by the treating team and at 24 (plus or minus 6) hours by the site investigator. If thrombosis or seizure is suspected, prompt treatment will be administered per the routine of the

treating facility. All study centers are tertiary care facilities with substantial pediatric and pediatric trauma expertise and are well prepared to evaluate and treat any complications that might arise.

All subjects discontinued early from the study protocol will have a reason for the early discontinuation recorded on the appropriate case report form, and the circumstances leading to discontinuation will be briefly described. All adverse events (as described) leading to discontinuation of study interventions will be fully documented and followed up as appropriate.

Subjects who are discontinued early from the study protocol are not considered to be withdrawn from the study, and will be included in the intention-to-treat analyses.

7.7 Potential Benefits

Future patients with significant traumatic injuries will benefit from the study if the results determine that TXA decreases complications from bleeding including the need for blood transfusions and improves the patients quality of life.

7.8 Withdrawal from Study

For participants who withdraw from the study, the date and reason for consent withdrawal must be documented. Otherwise, all subjects are followed for 180 days or death, whichever comes first, regardless of whether or not a subject has completed the study intervention. It is important for safety to follow all subjects. Therefore, research staff will confirm participants/parents wishes if they express the desire to withdrawal.

8 Data and Safety Monitoring Plan

8.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB) approved by the funding agency. The DSMB will be composed of a minimum of 5 members. The membership will include representation from experts in the fields of pediatric trauma care, biostatistics, bioethics, emergency medicine, and pediatric neurosurgery. The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as applicable.

The purpose of the DSMB is to advise the sponsors and principal investigator(s) regarding the continuing safety of study subjects and the continuing validity and sci-

entific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Centers, review of serious adverse events and other subject safety issues.

The DCC will send reports relating to these topics to DSMB members prior to each DSMB meeting. The DCC will staff the DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB prior to the end of the study. The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. When applicable, this will be sent directly to the study sponsor for approval before it is provided to the DCC and sites. When the summary is provided to the DCC, the DCC will send the summary to all Clinical Center investigators for submission to their respective Institutional Review Boards/Research Ethics Board(s).

8.2 Frequency of Interim Analysis

The DSMB will be expected to meet every six months, including an initial meeting prior to the start of subject enrollment and then after enrollment of the 10th subject (anticipated 2-3 months after onset of subject enrollment). The DSMB, however, will have the discretion to alter meeting timing and frequency.

8.3 Conflict of Interest

As described in the DSMB charter, DSMB members should be independent of all entities sponsoring, organizing, conducting, or regulating the TIC-TOC study. Specifically, DSMB members should not have any significant financial interest in the studys conduct or outcome, nor be involved in the design of this study. Additionally, members must disclose any actual or potential conflicts of interest involving pharmaceutical or biotechnology companies and contract research organizations. This includes any financial arrangement, consultancy agreement (direct or via third party), research support, or any other relationship that could be construed as introducing potential bias to their role as a DSMB member.

The DSMB and NHLBI Program Officer will be responsible for determining whether any consultancies or financial interests of a member may be viewed as potentially materially impacting their objectivity. This decision is to be based on the reasonable belief that objectivity is in doubt. Each DSMB member is responsible for informing the NHLBI Program Officer and DSMB Chairperson if any relevant changes in financial interest or

other developments affecting potential or perceived conflict of interest develop during the duration of DSMB membership.

8.4 Adverse Event Reporting

Assuring patient safety is an essential component of this protocol. Each participating site investigator will have primary responsibility for the safety of the individual subjects under his or her care. All adverse events occurring after study randomization through Day 7 or hospital discharge (whichever comes first) will be recorded and entered into the electronic data entry system provided by the DCC. In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the DCC.

8.4.1 Definitions, Relatedness, Severity and Expectedness

Definition: An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. The site investigators will evaluate for adverse events throughout the study period. Adverse events not previously documented in the study will be recorded on the adverse event record form. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment should be established.

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may **not** be assessed by a research coordinator, and must be assessed by an investigator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Some toxicities will be difficult to distinguish from abdominal symptoms related to acute gastroenteritis (such as bloating, abdominal pain, diarrhea, fever and diaper rash), and only at the time of analysis will we be able to determine whether these signs and symptoms are different between the groups.

Seriousness: The severity of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the subject was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An adverse event is considered expected if it is known to be associated with TXA, other underlying medical conditions of the subject, is known to occur with trauma, is directly related to study outcome, or is otherwise mentioned in the protocol, informed consent, or other study documents. An adverse event is unexpected when it is not expected as above or occurs in a differing severity or frequency than is described above.

Expected complications of traumatic injuries include all of the following: seizures, venous thromboses (including pulmonary emboli), acute kidney injuries (including kidney failure), pneumonia, acute lung injury, sepsis, and death. In addition, all items in the drug insert and all events associated with transfusion.

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Intervention: Surgery or procedure
- Other Treatment: Medication initiation, change, or discontinuation
- None: No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the subject returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

8.4.2 Time Period for Adverse Events

For purposes of this study, adverse events will be recorded for the period following randomization through hospital discharge or 7 days (whichever comes first). Events that occur prior to onset of study drug administration will not be considered adverse events. These events will be recorded as baseline conditions. Events that occur following hospital discharge will not be recorded. Adverse events will be followed until resolution or hospital discharge, whichever is earlier.

8.4.3 Data Collection Procedures for Adverse Events

After subject randomization, all adverse events (including serious adverse events), whether anticipated or unanticipated, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition present at the time of randomization, recorded in the subject's baseline history at study entry, which remains unchanged or improves, will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new adverse event and reported.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal at the time of randomization and that do not worsen will not be recorded as adverse events.

Because severe trauma is associated with a large number of laboratory abnormalities, for purposes of this study, abnormal laboratory values will be recorded as adverse events when the severity grade is grade 2 or higher on the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Grade 1 laboratory abnormalities, if expected as described earlier, do not need to be recorded as adverse events. It is not necessary to record abnormal laboratory results for those tests included in the Schedule of Evaluations because all values for these parameters will be collected. If an abnormality of a laboratory

parameter is considered to be serious by the site investigator, however, it will be necessary for the site to record and report the event as an SAE.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center because this requires specific training.

8.4.4 Unanticipated Problems (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized.

The site investigator will report unanticipated problems to the Data Coordinating Center within 24 hours. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event. After receipt of the complete report, the Data Coordinating Center will report these unanticipated problems to the NHLBI Program Official or Project Officer in an expedited manner (within 24 hours).

In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center.

In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and NHLBI staff cannot be reached expeditiously, the Data Coordinating Center will notify the principal investigators (Drs. Nishijima, Kuppermann) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

8.4.5 Monitoring Serious Adverse Events

The Principal Investigator of the Data Coordinating Center (Dr. Dean) will act as the medical monitor for this study. If Dr. Dean is unavailable, a qualified physician will be designated to fulfill this function.

Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign each SAE report after review.

All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by DSMB members and NHLBI staff.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, NHLBI staff and the DSMB chairperson will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the NHLBI staff and the DSMB chairperson cannot be reached expeditiously, the Data Coordinating Center will notify the principal investigators (Drs.Nishijima, Kuppermann) and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the NHLBI staff after discussion with the DSMB.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

After notification of the NHLBI Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the principle investigators (Drs. Nishijima, Kuppermann) and all clinical investigators, who will be instructed to report this to their local IRB.

The DSMB will review all adverse events (not necessarily serious, unexpected, and study-related) during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of Adverse Events for the DSMB meetings, classified with the MedDRA coding system.

8.4.6 Follow-up of Serious, Unexpected and Related Adverse Events

All serious, unexpected and related adverse events that are unresolved at the time of the subject's termination from the study or discharge from the hospital will be followed by the Clinical Center investigators until the events are resolved, subject is lost to follow-up, the adverse event is otherwise explained, or has stabilized.

9 Study Training

9.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study

procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the principal investigators (Drs. Nishijima, Kuppermann), will be the main contact for study questions. Follow-up assessments including PedsQL and GOS-E Peds, as well as digit span testing, will be performed by qualified staff at the University of California, Davis.

An in-person meeting will be held to review study activities, study workflow, and data entry procedures. Each site investigator should instruct the group of ED physicians at their home institutions about the study, and serve as local advocates and champions for the study and answer questions as they arise. Throughout the study, the study team will also have telephone conference calls, webinars, and in-person meetings to update on study progress and provide on-going training.

9.2 PECARN Network Involvement

This proposed pilot study of TXA for children with hemorrhagic torso injuries and traumatic intracranial hemorrhage will be completed within PECARN.[86]

PECARN is the first and only federally-funded pediatric emergency medicine research network in the United States, initially funded in 2001 through cooperative agreements between academic medical centers and the Health Resources Services Administration / Maternal and Child Health Bureau / Emergency Medical Services for Children Program (HRSA / MCHB / EMSC). PECARN was created to address barriers to research in emergency medical services for children (EMSC), including the lack of an infrastructure. PECARN conducts high-priority, multi-institutional research on the prevention and management of acute illnesses and injuries in children. Currently PECARN is comprised of 6 research nodes, an EMS research node containing 3 EMS affiliates, and a DCC. Each of the 6 research nodes has 3 hospital ED affiliates and one EMS affiliate. Overall, the PECARN EDs serve approximately 1.1 million acutely ill and injured children annually in the US.

The PECARN network is governed by a Steering Committee that formulates and monitors policies and procedures guiding all research activities and reviews and approves research proposals. All major scientific decisions are made by majority vote. Subcommittees, including the Protocol Review and Development Subcommittee (PRADs), the Grant Writing and Publications Subcommittee (GAPS), the Feasibility and Budget Subcommittee (FAB), and the Quality, Safety, and Regulatory Affairs Subcommittee (QUASI)

carry out specific tasks identified by the Steering Committee. This pilot project has been reviewed and approved by PECARN.

10 Regulatory Issues

10.1 Food and Drug Administration

This trial is being conducted under an Investigational New Drug application approved by the Food and Drug Administration (Investigational New Drug application #128206). The clinical investigator at each participating site will complete a Form FDA 1572, "Statement of Investigator."

10.2 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate subject age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

10.3 Inclusion of Women and Minorities

There will be no exclusion of subjects based on gender, race, or ethnicity.

10.4 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

10.5 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)]. In such cases where local regulations require that records be kept longer than the Federal Regulations require, records will be retained for the duration required by the local regulations.

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