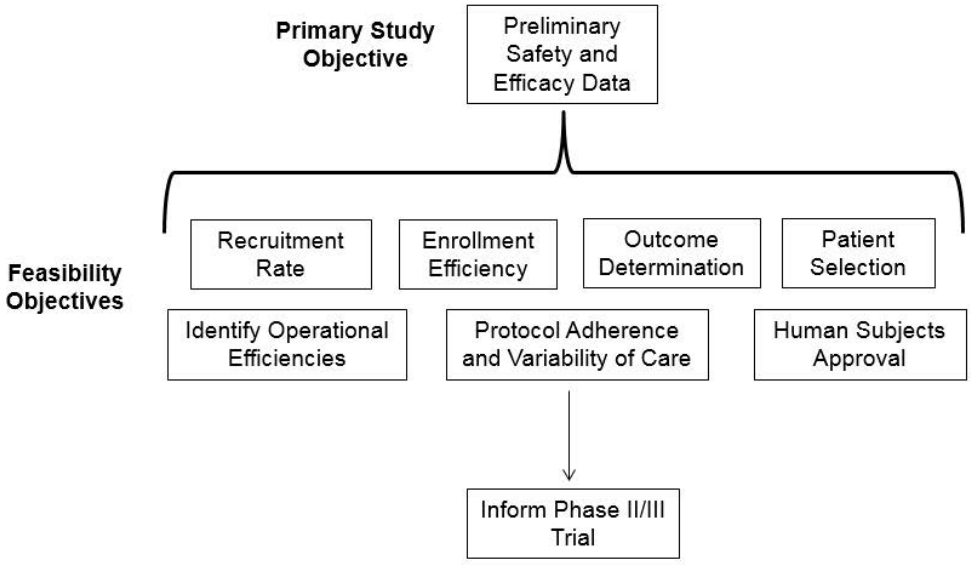

Figure 1: Schema of Study Objectives

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

"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

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

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).

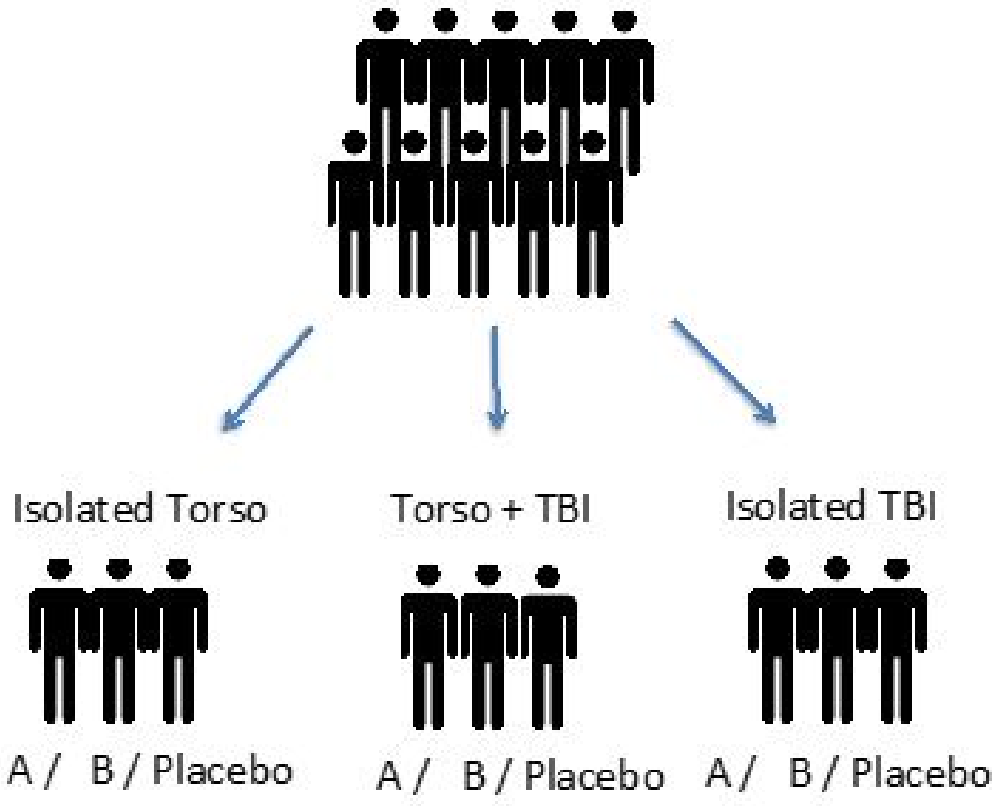

Figure 10: Block Randomization

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

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)

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

- 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

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).

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.

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.

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

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.