A Pediatric Trial Using Tranexamic Acid in Thrombocytopenia

A Prospective Single-Center, Double-Blinded, Randomized Study to Evaluate the Feasibility of using Tranexamic Acid to Reduce Bleeding Complications in Pediatric Patients with Hypoproliferative Thrombocytopenia.

Version 3.0
Version Date: 12 January 2020
NCT03806556

Protocol Synopsis

Patients receiving chemotherapy are at high risk of bleeding complications during the course of therapy, due to a variety of contributing factors. These include, but are not limited to the effects of thrombocytopenia, platelet dysfunction, vascular defects, coagulopathy and the adverse effects of medications received during the course of therapy [1]. Prior reviews on the subject have concluded that major bleeding episodes are associated with increased mortality rates, greater utilization of resources and an increased transfusion requirement [2]. Risks may be even greater in the pediatric population. The Determination of the Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients (PLADO) trial enrolled 200 pediatric patients, and found that the population of pediatric patients under study had a greater risk of bleeding events when compared to the adult patients. Bleeding occurred in up to 88% of pediatric patients despite the use of a prophylactic platelet transfusion threshold of ≤10,000/uL [3].

The appropriate strategy to address this risk is unclear. Prophylactic platelet transfusions are associated with a reduction in clinically significant bleeding compared to a therapeutic transfusion strategy [4]. However, trials evaluating the effectiveness of higher platelet transfusion thresholds have not demonstrated a commensurate decrease in bleeding incidence or severity [5-7]. Other strategies have included the use of higher dose platelet transfusions, which have also been found to be ineffective [8]. Therefore, alternative strategies to prevent bleeding events in thrombocytopenic patients must be identified to reduce the morbidity, mortality and increased transfusion requirements associated with such events.

Tranexamic Acid is a competitive inhibitor of plasminogen activation and inhibits fibrinolysis. It is available in an intravenous formulation and has been used in pediatric patients to prevent or reduce bleeding in the peri-operative setting, pediatric trauma and with menstrual bleeding [9-14]. Prior studies investigating the use of antifibrinolytic agents in patients with hypoproliferative thrombocytopenia have been limited, but results are encouraging as to its effectiveness [15-18]. However, none of these studies have included pediatric patients to date.

The results of this study will allow the investigators to evaluate recruitment success in order to plan for a larger trial to investigate the efficacy of tranexamic acid in this population. It will also provide evidence as to the safety of tranexamic acid when used as an adjunct to platelet transfusion in pediatric patients with hypoproliferative thrombocytopenia, and may provide a signal as to its effectiveness. Lastly laboratory studies will demonstrate whether the dose strategy for TXA effectively suppresses *in vitro* measures of fibrinolysis. If beneficial, this treatment could potentially lead to a decrease in bleeding episodes and platelet transfusions (with an attendant decrease in transfusion related adverse events) as well as potential savings for healthcare-related costs and improved quality of life.

Objectives
The purpose of this study is to evaluate the feasibility and safety of a randomized controlled trial of tranexamic acid for use in the prevention of bleeding complications in pediatric patients with hypoproliferative thrombocytopenia secondary to chemotherapy or blood and marrow transplantation. A secondary objective is to demonstrate that the TXA dosing strategy suppresses in-vitro measures of fibrinolysis.

Study Design
This will be a double blind, randomized, placebo-controlled trial. Eligible subjects will be identified by research staff or primary physicians after being identified as likely to have platelet counts of ≤20,000/uL for 5 days or longer. Daily assessments of hemostasis and thrombosis will be conducted via chart review, patient interviews and physical exams.

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Section 1. Summary

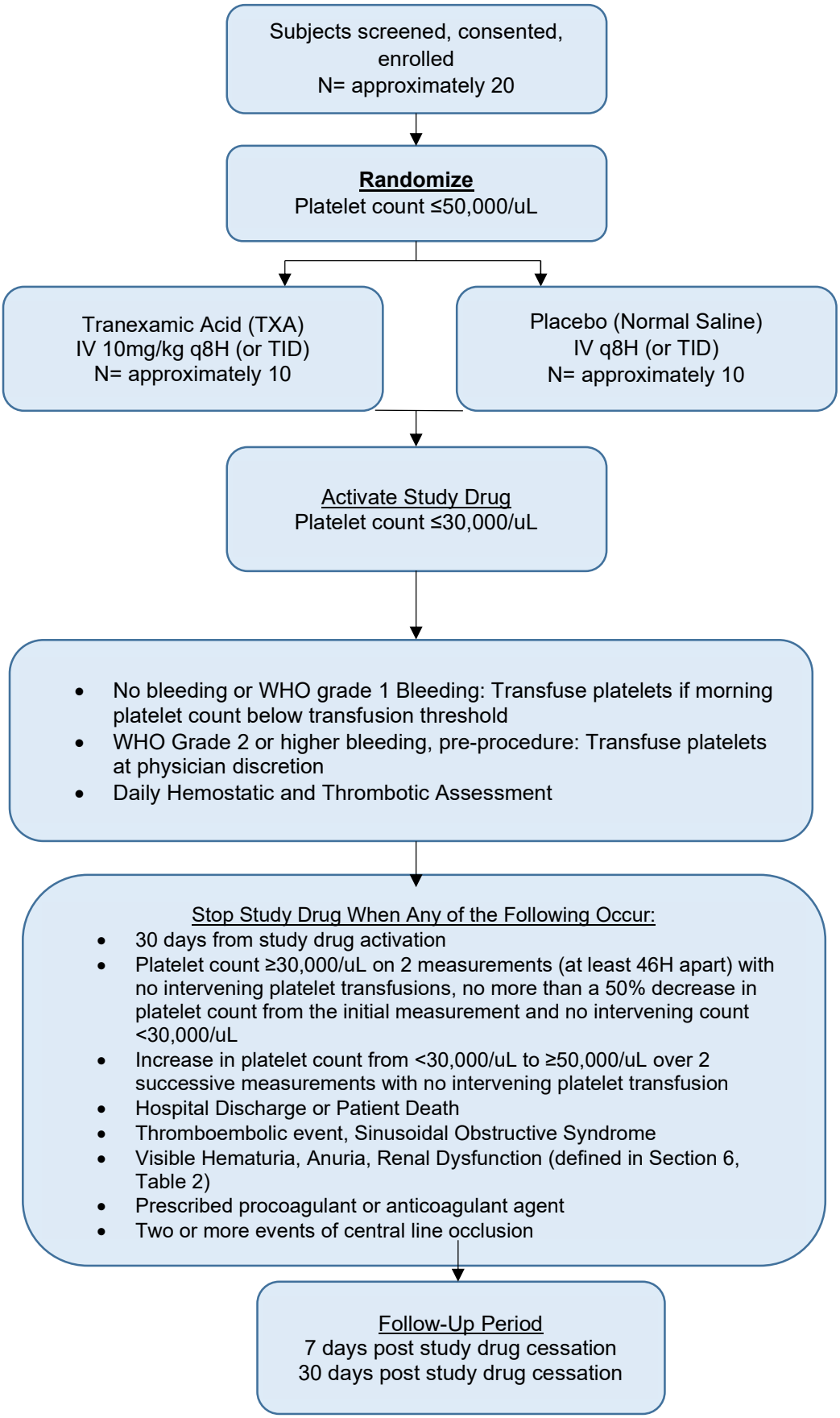
Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov TBD
Date of registration in primary registry	
Source(s) of monetary or material support	Internal
Contact for public queries	*Meghan McCormick*, MD, [201-919-6793] [Meghan.mccormick3@chp.edu] *Darrell Triulzi,* MD [DTriulzi@itxm.org]
Contact for scientific queries	*Meghan Mccormick*, MD The Children's Hospital of Pittsburgh of UPMC Pittsburgh, PA, USA
Public title	A Pediatric Trial Using Tranexamic Acid in Thrombocytopenia
Scientific title	A Prospective, Single-Center, Double-Blinded, Randomized Study to Evaluate the Feasibility of using Tranexamic Acid to Reduce Bleeding Complications in Pediatric Patients with Hypoproliferative Thrombocytopenia
Countries of recruitment	USA
Health condition(s) or problem(s) studied	Thrombocytopenia, Malignancy

Data category	Information
Intervention(s)	Active comparator: Tranexamic Acid 10 mg/kg IV q8H (or TID if preferred by primary physician) Placebo comparator: Normal Saline IV q8H (or TID if preferred by primary physician)
Key inclusion and exclusion criteria	Ages eligible for study: ≥2 years, ≤21 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria (all must be present): • Patient hospitalized • Confirmed diagnosis of hematologic malignancy or solid tumor • Undergoing or planned chemotherapy or blood or marrow transplantation • Expected period of thrombocytopenia resulting in platelet count of ≤20,000/uL for ≥ 5 days • Requires platelet transfusion threshold ≤30,000/uL • >14 days beyond last dose of PEG-Asparaginase or >72 hours beyond last dose of Erwinia Asparaginase Exclusion criteria (none must be present): • Diagnosis of acute promyelocytic leukemia • History of ITP, TTP or HUS • Known inherited or acquired bleeding disorder

Data category	Information
	• Known inherited or acquired prothrombotic disorder • Diagnosis of DIC • WHO Grade 2 or greater bleeding within 48 hours prior to enrollment or study drug activation • Receipt of PEG-asparaginase within 7 days prior to enrollment • Receiving tranexamic acid (or other anti-fibrinolytic agent) or any other pro-coagulant agent; Receiving estrogen derivatives or progestins • Receiving therapy with anticoagulation or antiplatelet therapy • Receiving platelet growth factors • History of thromboembolic event within past six months • History of sinusoidal obstruction syndrome • Visible hematuria • Renal dysfunction (as defined in Section 6, Table 2), receiving dialysis or anuria (defined as <10mL/hr urine over 24H) • History of seizures • Known allergy to tranexamic acid • Pregnancy • Receiving outpatient therapy or predicted to have inpatient hospital stay ≤3 days • Patient with platelet count ≥30,000/uL without predicted fall in platelet count
Study type	Interventional Allocation: randomized, 1:1 Intervention model: parallel assignment Masking: double blind (subject,

Data category	Information
	caregiver, investigator, outcomes assessor) Primary purpose: Prevention Phase I Study Period: 18 months
Date of first enrollment	TBD
Target sample size	20
Recruitment status	Pre-Recruitment
Primary outcome(s)	Determine the feasibility of enrolling and conducting an RCT of tranexamic acid in pediatric patients with hypoproliferative thrombocytopenia To define and describe safety of tranexamic acid administered on this schedule To demonstrate appropriate suppression of in vitro fibrinolytic activity by tranexamic acid administered on this schedule
Key secondary outcomes	To preliminarily define the reduction in WHO grade 2 or higher bleeding events within the confines of a Phase 1 study To assess the reduction in number of platelet transfusions To assess the reduction in number of red blood cell transfusions

Figure 1. Study Schematic



2. Background

Patients receiving chemotherapy are at high risk of bleeding complications during the course of therapy, due to a variety of contributing factors. These include, but are not limited to the effects of thrombocytopenia, platelet dysfunction, vascular defects, coagulopathy and the adverse effects of medications received during the course of therapy [1]. Prior reviews on the subject have concluded that major bleeding episodes are associated with increased mortality rates, greater utilization of resources and an increase in transfusion requirements [2]. Risks may be even greater in the pediatric population. The Determination of the Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients (PLADO) trial enrolled 200 pediatric patients, and found that the population of pediatric patients under study had a greater risk of bleeding events when compared to adult patients. Bleeding occurred in up to 88% of pediatric patients despite the use of a prophylactic platelet transfusion threshold of ≤10,000/uL [3].

The appropriate strategy to address this risk is unclear. Prophylactic platelet transfusions have been shown to lead to a reduction in clinically significant bleeding compared to a therapeutic transfusion strategy [4]. However, trials evaluating the effectiveness of using a high platelet transfusion threshold have not demonstrated a commensurate decrease in bleeding incidence or severity [5-7]. Other strategies have included the use of higher dose platelet transfusions, which have also been found to be ineffective in reducing the incidence of bleeding [8]. A single-institution study of blood product transfusion requirements in a pediatric hematology/oncology population found that 66% of patients received transfusion of red blood cell or platelet products during the study period [19]. The burden associated with blood product transfusions includes the risk of adverse effects associated with transfusion, affecting up to 10% of transfusions [20]. Multiple platelet transfusions can also be associated with significant costs, in 2018 Medicaid set reimbursement for a unit of irradiated, leukoreduced red blood cells at $167.64. Therefore, alternative strategies to prevent bleeding events in thrombocytopenic patients must be identified to reduce the morbidity, mortality and increased transfusion requirements associated with such events.

Anti-fibrinolytic agents, including Tranexamic Acid and Aminocaproic Acid, are competitive inhibitors of plasminogen activation and inhibit fibrinolysis. Tranexamic acid is available in an intravenous formulation and has been used in pediatric patients to prevent or reduce bleeding in the peri-operative setting, cases of trauma and with menstrual bleeding [9-14]. Prior studies investigating the use of antifibrinolytic agents in patients with hypoproliferative thrombocytopenia have been limited, but results are encouraging as to its effectiveness [15-18]. However, many of these studies have been small and did not include pediatric patients. At this time there are multiple large randomized controlled trials underway investigating whether antifibrinolytic agents can mitigate the incidence of bleeding and transfusion in patients with malignancies receiving chemotherapy. However, these are limited to adult participants. Given that the rate of bleeding events is even greater in the pediatric population, it stands to reason that antifibrinolytics may be beneficial in this population as well.

The dose of tranexamic acid chosen for this study, 10mg/kg q8H or TID, was chosen from the package insert for Tranexamic Acid, and has been safely used in pediatric patients for other indications. One of the major concerns regarding the use of antifibrinolytics is their theoretical risk of thromboembolic events. Tranexamic acid has been used widely in several major studies, including the CRASH-2 trial and the WOMAN trial, neither of which showed evidence for an increased risk of thromboembolic event in participants receiving tranexamic acid versus placebo [21, 22]. In order to provide an additional layer of caution we will also plan to exclude all patients with a current or past history of thromboembolic disease, current bleeding or coagulation disorders.

Additionally, this study will incorporate a secondary translational component utilizing assays of fibrinolysis on samples obtained from patients prior to and following antifibrinolytic therapy. As this study will not be adequately powered to detect differences in the occurrence of bleeding events between patients in the treatment group and the placebo group, identification of the successful impairment of fibrinolysis *in vitro* will provide evidence of adequate antifibrinolytic dosing. Additionally, by better characterizing baseline fibrinolytic activity in pediatric patients with malignancies, this may allow us to identify a subset of patients in whom antifibrinolytic therapy may be the most useful.

3. Study Aims and Endpoints

3.1 Primary Aims and Endpoints

Aim 1: To determine the safety and feasibility of the use of tranexamic acid in pediatric patients receiving chemotherapy or blood and/or marrow transplantation (BMT)
Endpoint: Incidence of adverse events, serious adverse events and death attributed to study drug; Number of patients screened eligible for enrollment and the rate of recruitment during study period

Aim 2: To evaluate the effectiveness of current dose of tranexamic acid for suppressing *in vitro* fibrinolysis
Endpoint: Measures of fibrinolytic activity at baseline (prior to tranexamic acid infusion) and at steady-state

3.2 Secondary Aims and Endpoints

Aim 3: To determine whether tranexamic acid leads to a decrease in the incidence of WHO Grade 2 or higher bleeding events
Endpoint: Proportion of patients with WHO Grade 2 or higher bleeding events daily following activation of study drug or placebo

Aim 4: To determine whether tranexamic acid leads to a reduction in the number of days with any grade bleeding event
Endpoint: Proportion of patients with any grade bleeding event following activation of study drug

Aim 5: To determine whether tranexamic acid leads to a decrease in the highest observed grade of bleeding (as measured on WHO bleeding scale) during the study period
Endpoint: Highest grade of bleeding (as measured on WHO bleeding scale) during study period in each enrolled patient

Aim 6: To determine whether tranexamic acid leads to a reduction in the number of red blood cell or platelet transfusions required
Endpoint: Number of red blood cell or platelet transfusions per patient daily following activation of study drug

Aim 7: To determine whether tranexamic acid prolongs the amount of time from activation of study drug to the first episode of WHO Grade 2 or higher bleeding
Endpoint: Length of time from activation of study drug to first episode of WHO Grade 2 or higher bleeding

3.3 Safety Endpoints

Adverse events and serious adverse events will be monitored and collected from the time of activation of the study drug until a period up to and including 30 days after the last dose of the study drug. Adverse events and serious adverse events will to be assessed by CTCAE v.4.0 criteria and compared between study drug and placebo arms. The following events will specifically be compared across study arms;

- Incidence of thrombotic events (A thrombotic event is defined as venous or arterial thrombosis confirmed on imaging study, which may include Doppler US, CT scan, MRI or venography)
- Incidence of veno-occlusive disease (also known as sinusoidal obstruction syndrome)
- All cause-mortality, including incidence of death due to thrombosis

4. Population

Pediatric patients with hematologic malignancy or solid tumors receiving chemotherapy or undergoing BMT.

4.1 Inclusion Criteria

Patients eligible for trial must comply with all of the following at the time of randomization:

- Patients must be ≥2 years of age and ≤21 years of age
- Patients must have a confirmed diagnosis of hematologic malignancy or solid tumor malignancy
- Patients must be undergoing or planned chemotherapy or BMT
- Patients will only be eligible to receive study drug or placebo during a predicted inpatient stay of ≤3 days
- Patients must be predicted to have thrombocytopenia ≤20,000/uL for ≥5 days
- Patient must have a platelet transfusion threshold of ≤30,000/uL
- Patients must be >14 days beyond their last dose of PEG-Asparaginase or >72 hours beyond their last dose of Erwinia Asparaginase (with exceptions below)

- Patients must be able to comply with treatment and monitoring

4.2 Exclusion Criteria

To be eligible for participation in the study, potential subjects must not meet any of the following criteria:

- Diagnosis of acute promyelocytic leukemia
- History of ITP, TTP or HUS
- History of inherited or acquired bleeding disorder
- History of inherited or acquired prothrombotic disorder
- Diagnosis of DIC
- Patient must not have WHO Grade 2 bleeding or greater within 48 hours prior to enrollment or study drug activation
- Patient must not have received PEG-Asparaginase within the 7 day period prior to enrollment. If this product is given within the 8-14 day period prior to enrollment patients are eligible if PT, PTT, INR and fibrinogen are obtained and are within 1.5 times the upper limits of normal.
- Patient must not be receiving tranexamic acid or other anti-fibrinolytic agent or any other agent to promote hemostasis (which includes DDAVP, recombinant Factor VII, Prothrombin Complex Concentrate, Estrogen Derivatives and Progestins)
- Patient must not be receiving therapy with anticoagulation or antiplatelet therapy (which includes heparin infusion, enoxaparin, aspirin. If anticoagulant/antiplatelet therapy is discontinued when platelet count is <50,000/uL patient will be eligible for enrollment)
- Patient must not be receiving platelet growth factors
- Patient has a current/prior history of thromboembolic event within the past six months. If history of thromboembolic event the patient should be >30 days from completion of anticoagulation therapy
- Patient has a current/prior history of sinusoidal obstruction disease
- Patient has visible blood in their urine
- Patient with renal dysfunction (defined in Section 6, Table 2), hemodialysis or with anuria (defined as <10mL urine/hour over 24 hours)
- History of seizures
- Allergy to tranexamic acid
- Pregnancy
- Unwilling to accept blood transfusions
- Requires platelet transfusion threshold higher than study protocol (If the patient is enrolled on study and begins treatment with either the study drug or placebo, and subsequently requires a platelet transfusion threshold greater than the study protocol they will remain on study).

5. Trial Enrollment

5.1 Screening and Recruitment

Potentially eligible subjects will be identified by the investigator or trained member of the research staff. All new admissions to the Oncology or Bone Marrow Transplantation

service will be screened on a daily basis for potential eligibility based on underlying diagnosis and an expected period of thrombocytopenia ≤20,000/uL lasting ≥5 days. Patients who will be undergoing BMT may also be identified by their primary transplant physician at the time of their consent for BMT. Following initial identification of eligibility, the primary investigator or member of the research staff will screen subjects for full enrollment eligibility using medical history and laboratory results. There will not be a screening consent, we will seek a waiver of consent for screening purposes only. Screening eligibility checklist will be maintained in trial file in order to track information on screening and consent metrics at trial end. There will be no identifiable protected health information recorded on screening forms for patients who do not meet eligibility requirements or who decline trial enrollment. Patients who are screened for eligibility and meet requirements will be assigned a case ID which will be used to identify the participant on all subsequent trial documentation. The names of all patients screened for eligibility will recorded on a separate screening log sheet in order to avoid double-screening.
After obtaining permission from the subject's physician to discuss the study, the primary investigator or trained research staff member will contact the prospective subject and obtain study consent. After signing the study consent the subject will be enrolled on to the study.

5.2 Randomization

This trial is designed as a prospective, randomized, controlled, blinded (patient, caregiver, physician, assessor) trial with two parallel groups and a primary endpoint of feasibility and safety. Randomization will be performed as block randomization with a 1:1 allocation within blocks of size four.

When a consented participant's platelet count falls to ≤50,000/uL and the platelet count is expected to continue to fall and remain ≤20,000/uL for 5 days or longer, the patient will be randomized to either the tranexamic acid arm or the placebo arm by the investigational pharmacy. When the randomized subject's platelet count is ≤30,000/uL with an expectation that the platelet count will be ≤20,000/uL for 5 days or longer the study drug will be activated. Activation of the study drug will act as time point zero for all study endpoints.

5.3 Enrollment Period

Screening will continue until the target population is achieved (20 activated subjects total). The enrollment period will extend over 18 months. The expected enrollment is estimated to be 14 randomized subjects per year. Both arms will have a target enrollment of 10 activated subjects

6. Interventions

6.1 Study Drug (Tranexamic Acid or Placebo)

Tranexamic acid forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. Patients who are randomized to receive tranexamic acid will receive 10mg/kg IV Q8h by default, TID dosing will also be acceptable if it allows for fewer breaks into the line to reduce the risk of central-line associated

infections. Patients will continue tranexamic acid until they meet criteria for stopping the study drug as provided in section 6.3. Criteria for temporary discontinuation of the study drug are given in section 6.4.

Tranexamic acid is a clear, colorless liquid in IV form. Patients randomized to the control arm will receive matching placebo, which will be IV normal saline of a volume equivalent to what the patient's dose of tranexamic acid would be.

Rationale for dose:
According to the Children's Hospital of Pittsburgh formulary through Lexicomp, the dosing of tranexamic acid for use in prevention of bleeding associated with tooth extraction in hemophilia patients is 10mg/kg three to four times daily by IV. For the prevention of bleeding associated with surgical procedures (cardiac and spinal procedures) continuous IV infusions of tranexamic acid have been used. In pediatric cardiac surgery, TXA dosing ranges from 100mg/kg IV bolus followed by a continuous infusion of 10mg/kg/hour IV infusion to a loading dose of 6.4mg/kg followed by a continuous infusion in the range of 2 to 3.1mg/kg/hour. In pediatric non-cardiac surgery the range of doses used in pediatric randomized trials is shown below. They range from 100mg/kg IV load following by a continuous infusion of 10mg/kg/hour to 10mg/kg IV load to 1 mg/kg/hour infusion in in pediatric patients undergoing spinal surgery [12, 23-26]. Long-term prophylaxis in children with hereditary angioedema uses doses of 20 to 75mg/kg/day in two to three divided doses, administered orally. In cases of traumatic hyphema, tranexamic acid is dosed orally at 25mg/kg/dose every eight hours for five to seven days.

The dose chosen for this study is in the low -range of recommended IV doses for pediatric indications.

Table 1: Tranexamic acid dosing in pediatric non-cardiac surgery trials

Author	Design	Number	Age	Dose	Effect
Neilipovitz 2001	TXA vs placebo (RCT)	44	8-18	10mg/kg 1mg/kg/hr	Significant reduction in blood loss -250mls (-1123 to 623mls)
Sethna 2005	TXA vs placebo (RCT)	40	9-18	100mg/kg 10mg/kg/hr	Significant reduction in blood loss -855mls (-1408 to -301mls) NS reduction in blood transfusion 0.85 (0.56-1.30
Ng 2016	TXA vs placebo (retrospective cohort)	90 (55/35)	10-23	100mg/kg 10mg/kg/hr	Blood loss decreased by 1.8L vs 3.9L p<0.01, blood transfusion decreased by 77%
Goobie 2011	TXA vs placebo (RCT)	43	2 months – 6 years	50mg/kg 5mg/kg/hr	Significant reduction in blood loss 65mls/kg vs 119mls/kg and blood transfusion 33 vs 56mls/kg
Dadure 2011	TXA vs placebo (RCT)	40	3-15 years	15mg/kg 10mg/kg/hr	Significant reduction in blood loss 7.2mls/kg vs 16.6mls/kg NS reduction in blood transfusion 37% vs 70%

6.2 Concomitant Care

Patients enrolled on trial must have a prophylactic platelet transfusion threshold of ≤10,000/uL (for patients with solid tumors or hematologic malignancies not undergoing BMT) or ≤20,000/uL (for patients undergoing BMT) at the time of randomization. Prophylactic platelet transfusions will be given when morning platelet count is below the above values for prophylactic transfusions. Therapeutic platelet transfusions above these thresholds will be allowed at the discretion of their treating physician (for cases including active bleeding, for an expected platelet count of ≤10,000 or ≤20,000/uL the following morning, planned invasive procedures with the need for an increased platelet threshold or trauma). Clinicians will be allowed to exercise discretion to transfuse platelets for any reason should they feel there is a clinical reason to do so. In cases where a platelet transfusion is given for invasive procedures or trauma the subject will return to the study platelet transfusion threshold following this event when determined safe to do so by the treating physician. If, following enrollment and study drug activation, the subject subsequently has an event which leads to the need for a platelet transfusion threshold of greater than the study protocol, they will remain on study.

Type and dose of platelet transfusion will not be specified. If a patient appears to develop platelet refractoriness (which is defined as two sequential transfusions with a repeat platelet count after a 4hour period of ≤5000/uL) then clinicians may exercise their judgement as to use of matched platelets or alloantibody testing. Data on type of platelet transfusion administered will be collected. For any platelet transfusions given

above the study threshold the rationale will be recorded on the daily transfusion assessment form.

Patients will receive red blood cell transfusions as per the standard care of their treating physician.

No other medication changes are directed in this protocol and standard care will otherwise be followed.

6.3 Stopping Points

The patient's physician or the principal investigator may withdraw the patient from the study for any reason. An End of Study form will be completed with the reason for withdrawal documented in such an occurrence.

The study drug will be permanently discontinued in one of the following circumstances:

- The participant meets an exclusion criteria (either newly developed or not recognized previously) that precludes further study participation
- The patient has been on study drug or received placebo medication for 30 days from the date of study drug activation
- The patient's platelet count increases spontaneously from <30,000/uL to ≥50,000/uL across two successive platelet measurements with no intervening platelet transfusion
- The patient's platelet count remains ≥30,000/uL on 2 measurements made at least 46 hours apart without intervening platelet count of <30,000/uL or a decrease in platelet of greater than 50% between two measurements and without intervening platelet transfusion
- The patient is prescribed any other procoagulant, antiplatelet or anticoagulant agent by their treating physician (this includes open label tranexamic acid)
- The patient is discharged from hospital admission
- The patient experiences a thrombotic event
- The patient develops sinusoidal obstructive disease
- The patient develops visible hematuria, renal dysfunction (as defined in Section 6, table 2) or anuria
- The patient has a recurrent incident of complete central line occlusion: defined as the inability to access or infuse through a central line requiring instillation of fibrinolytic agent such as alteplase for clearing. This does not include lines that require certain patient positioning for instillation of agents, which suggest a "kink" in the line. A recurrent incident is when the definition is met on 2 separate occasions while receiving study drug.
- The patient becomes pregnant

If any of the above reasons lead to cessation of the study drug it should not be restarted even if the patient later meets criteria again for the study drug.

Subjects have the right to withdraw consent at any time. If a patient withdraws their consent for further participation, the subject will be asked to grant consent for the study

team to passively monitor their outcomes for major clinical events. For each patient at the end of therapy, the date and time that the study drug is voluntarily stopped will be recorded, along with the reasons that the subject so elected. It will be documented whether the subject is:

- Stopping study drug, but will continue to follow all other study-defined procedures and monitoring
- Stopping study drug and study-defined procedures and monitoring but allows investigators to passively monitor their medical record and follow-up for vital status up to 30 days after their last dose of study drug.
- Discontinuing all further contact with study investigators

In the event of subject death, the date of death will be recorded on the study form and will be characterized by time from consent and according to whether the investigator attributes the mortality to bleeding, thrombosis or death from other cause.

When a patient meets one of the above study stopping criteria, the study medication will be discontinued following the next daily assessment.

6.4 Temporary Stopping Points

The study drug will be temporarily discontinued in the following situations:

- Diagnosis of DIC by the treating team or treating physician
- First event of central line occlusion (as defined above)

In these situations, as detailed above, the study drug may be restarted after resolution of the situation.

6.5 Organ Function Requirements

Dose adjustments for renal insufficiency are recommended according to the Children's Hospital of Pittsburgh Lexicomp formulary. As existing recommendations for dose adjustment are derived from the adult population and not for pediatric patients, the following table was created to guide participant exclusion based on renal function. The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

Table 2. Adequate Pediatric Renal Function:

Adequate renal function defined as:		
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m2 or		
- A serum creatinine based on age/gender as follows:		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8

6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

No dose adjustment is needed for hepatic impairment

7. Study Drug Information

7.1 Masking of Study drug

The investigational pharmacy at each trial site will randomize and distribute tranexamic acid or placebo (as an equal volume of normal saline). The manufacturers, batch numbers, and sources will be recorded for all doses. The pharmacy will use the commercially available product purchased for use by the formulary.

Although the investigational pharmacy will be unblinded, they will not share any blinded information with the study team except in case of emergency. Unblinded pharmacy staff will not be involved in patient or outcomes assessment.

Patients, care providers, study coordinators and study investigators will not be told which arm the patient is on. Among study personnel, only the unblinded pharmacists will have access to treatment assignment. The placebo will be normal saline administered by IV. Tranexamic acid in IV solution is clear and colorless and grossly similar to tranexamic acid in appearance. Research coordinators who collect outcomes data will have no contact with study drug.

7.2 Administration of Study Drug

The study drug will be started according to the randomization assignment after meeting activation criteria. The dosing schedule for tranexamic acid will be 10mg/kg every 8 hours (or TID dosing if preferred by primary physician). Tranexamic acid will diluted in normal saline to a total volume of 15mL. The dosing schedule for placebo will be an equivalent volume of normal saline (15mL) every 8 hours (or TID dosing if preferred by primary physician). Both TXA and placebo will be infused over 15 to 30 minutes, then the line is flushed with normal saline. Nursing staff will be instructed to document in the medical record if medication is not administered within the 15-30 minute infusion time, as well as the reason for this.

Tranexamic Acid does not have Y-site or admixture compatibility with Ampicillin, Blinatumomab, Penicillin or Pipercillin-Tazobactam. Tranexamic acid should not be mixed with blood products. Tranexamic acid may be mixed with most solutions for infusion such as electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions.

8. Study Procedures and Schedule

The following data will be collected according to the timeline below. If two or more study points fall on the same calendar day (for example if the date of consent and date of randomization are the same day) then all of the unique lab measurements required for

each time point need to be collected, but a lab measurement that is required at both time points does not need to be repeated twice.

8.1 Day of Enrollment

- Thrombotic Assessment
    - Assessment for thrombotic event will be performed via a review of medical chart notes and relevant imaging studies obtained within the time period from prior assessment. This definition of will apply to all future time points when a thrombotic assessment is completed.
- Demographics and Medical History
    - Weight, Height, BMI
    - Date of Birth
    - Gender
    - Ethnicity
    - Race
    - Primary Diagnosis
        - Including disease, current treatment (Radiation, chemotherapy medications, BMT source, Donor ABO Type and Related/Unrelated Donor)
    - ABO Type
    - Concomitant Medications
- Laboratory Assessment (lab studies obtained within 24H period prior to enrollment do not need to be repeated unless otherwise stated)
    - CBC
    - Serum Creatinine
    - Pregnancy Test (Urine or Serum, if female of child-bearing age and >72 hours from previous)
    - HLA Testing results (if done as part of routine care)
    - Coagulation Testing (PT, PTT, INR and Fibrinogen) if PEG-Asparaginase or Erwinia Asparaginase has been given >7 days but ≤14 days from date of enrollment
- Adverse events related to standard anticancer therapies will be carefully monitored for events that would preclude activation of study drug. Collection and documentation of AEs for the trial will begin following first dose of study drug.

8.2 Days Between Enrollment and Randomization; Days Between Randomization and Activation of Study Drug

- Thrombotic Assessment (via chart review), to be completed once weekly
- Laboratory Assessment, to be completed daily
    - CBC
- Adverse events related to standard anticancer therapies will be carefully monitored for events that would preclude activation of study drug. Collection and documentation of AEs for the trial will begin following first dose of study drug.
- Medication Review – Document new or discontinued medications

8.3 Day of Randomization

- Hemostatic/Bleeding Assessment
    - Bleeding will be recorded using the WHO Bleeding score as the bleeding assessment tool. Bleeding assessments will be completed by means of a physical assessment of the patient, patient interview and a review of patient chart and laboratory data for documented bleeding events. Research staff which will be either research nurse, primary investigator or co-investigator, will perform physical assessment of the patient and interview prior to reviewing the patient's medical chart and laboratory data to allow an objective assessment. Nursing staff may provide additional details. If participant has had WHO Grade 2 or higher bleeding within 48H of randomization they will not be randomized. They will be eligible for randomization if bleeding later resolves. This definition of hemostatic/bleeding assessment will apply to all further time points at which a bleeding assessment is completed.
    - If participant has had WHO Grade 2 or higher bleeding within 48H of randomization they will not be randomized. They will be eligible for randomization if bleeding later resolves.
- Thrombotic Assessment (via chart review)
- Laboratory Assessment (lab studies obtained within 24H period prior to randomization do not need to be repeated unless otherwise stated)
    - Coagulation Profile (PT, PTT, INR, Fibrinogen, D-Dimer)
    - CBC
    - Serum Creatinine
    - Pregnancy Test (Urine or Serum, if female of child-bearing age and >72 hours from previous)
    - Urinalysis (if >72 hours from previous)
- Data on Platelet Transfusions
    - Number of platelet units transfused
    - Source of platelet transfusions (apheresis or whole blood)
    - HLA or cross-match compatible
    - Reason for Transfusion
- Data on Red Blood Cell Transfusions
    - Number of units transfused
    - Reason for transfusion
- Adverse events related to standard anticancer therapies will be carefully monitored for events that would preclude activation of study drug. Collection and documentation of AEs for the trial will begin following first dose of study drug
- Medication Review – Document new or discontinued medications

8.4 Day 1 of Study Drug

- Hemostatic/Bleeding Assessment
    - If participant has had Grade 2 or higher bleeding within 48H of initiation of the study drug this should not be activated. They will be eligible for activation of the study drug later if bleeding later resolves.

- Thrombotic Assessment (via chart review)
- Laboratory Assessment (to be drawn prior to first dose of study drug)
    - CBC
    - Serum Creatinine
    - Urinalysis (if >72 hours from last Urinalysis)
    - Fibrinolysis study labs
- Data on Platelet Transfusions
    - Number of platelets transfused
    - Source of platelet transfusions (apheresis or whole blood)
    - HLA or cross-match compatible
    - Reason for transfusion
- Data on Red Blood Cell Transfusions
    - Number of units transfused
    - Reason for transfusion
- Adverse Event Assessment and Reporting – All Grade 3 or greater adverse events will be documented and followed
- Medication Review – Document new or discontinued medications

8.5 Days 2-30 of Study Drug

- Hemostatic/Bleeding Assessment
- Thrombotic Assessment (via chart review)
- Laboratory Assessment
    - CBC – to be drawn daily
    - Serum Creatinine – to be drawn daily
    - Bilirubin level – to be drawn once weekly
    - Fibrinolysis labs – to be drawn on Day 5 (+/- 1 day)
- Data on Platelet Transfusions
    - Number of platelets transfused
    - Source of platelet transfusions (apheresis or whole blood)
    - HLA or cross-match compatible
    - Reason for transfusion
- Data on Red Blood Cell Transfusions
    - Number of units transfused
    - Reason for transfusion
- Adverse Event Assessment and Reporting - All Grade 3 or greater adverse events will be documented and followed
- Medication Review – Document new or discontinued medications

8.6 Day 7 (+/- 3 days) and Day 30 (+/- 3 days) following Discontinuation of Study Drug

- Hemostatic/Bleeding Assessment (via phone conversation or clinic visit for patients who have been discharged; via chart review for patients who remain inpatient)
- Thrombotic Assessment (via phone conversation or clinic visit for patients who have been discharged; via chart review for patients who remain inpatient)

- Adverse Event Assessment and Reporting (via phone conversation or clinic visit for patients who have been discharged; via chart review for patients who remain inpatient). All Grade 3 or greater adverse events will be documented and followed

Table 3. Timeline for Study Assessment

Schedule of Events	Pre-Treatment Period					Treatment Period		Post-Treatment Period
Event	Pre-Screening	Day of Enrollment[1]	Days Between Enrollment and Randomization	Day of Randomization[1]	Days Between Randomization and Activation	Day 1 of Study Drug	Days 2-30 of Study Drug	Day 7 (+/- 3 days) and Day 30 (+/- 3 days) after Discontinuation of Study Drug
Medical Chart Review	X							
Informed Consent		X						
Demographics and Medical History		X						
ABO Type		X						
HLA Testing*		X						
Fibrinolysis Labs						X	X_2	
CBC		X	X	X	X	X	X	
Serum Creatinine		X		X		X	X	
Urinalysis				X_3		X_3		
Coagulation Profile (PT/PTT/INR/Fibrinogen/D-dimer)		X_4		X				

Pregnancy Test		X_5		X_5				
Bilurubin level							X_6	
Bleeding Assessment				X		X	X	X
Thrombotic Assessment		X	X_7	X	X_7	X	X	X
Data on Transfusion				X		X	X	
Drug or Placebo Administered						X	X	
Adverse Event Assessment						ongoing		
Medication Review	ongoing							

1. Lab studies obtained within 24H period prior to enrollment or randomization do not need to be repeated
2 To be collected at one time point on day 5 (+/- 1 day), at least six hours after administration of the last study drug dose and before the next dose due
3. Urinalysis does not need to be repeated if within 72 hours of previous.
4. If patient has received PEG-Asparaginase or Erwinia Asparaginase >7 and ≤14 days from day of enrollment collect PT, PTT, INR and Fibrinogen **only**
5 Urine pregnancy does not need to be repeated if within 72 hours of previous.
6 Once weekly while on study drug
7 To be completed once weekly by chart review
* If obtained as part of routine care

8.7 Fibrinolysis labs

Blood samples will be collected at two time points during the study period to assess suppression of fibrinolysis with study dose of tranexamic acid. At time point one, blood will be collected prior to first dose of study drug to measure baseline fibrinolytic activity. At time point two, blood will be collected at one time point on Day 4-6 of treatment, at least six hours after last dose of study drug and prior to next dose of study drug, in order to assess the suppression of fibrinolysis when tranexamic acid is present at steady state. Samples should be processed and frozen within 4-8 hours of collection. Samples will be stored at the Children's Hospital of Pittsburgh. They will be batched together and shipped to UNC Chapel Hill where fibrinolysis assays will be completed in such a way as to allow for minimum shipments. A portion of each patient's frozen sample will remain at the Children's Hospital of Pittsburgh for use in later biomarker assays of fibrinolysis (unless only minimum quantity required by UNC Chapel Hill has been drawn, in which case all of the sample will be shipped.) At UNC Chapel Hill samples will be

stored until fibrinolysis assays have been completed and then will be disposed of. Samples at the Children's Hospital of Pittsburgh will be stored indefinitely and used until exhausted. Study participants can request in writing that that samples no longer be used for research and any samples will be destroyed. Study sample may be used at later point for additional testing of the effects of tranexamic acid.

8.8 Laboratory procedures

The laboratory tests that will be performed as part of this study will be run in the hospital-based clinical laboratory and are standard in all hospital based clinical laboratories, with the exception of the fibrinolysis labs. Fibrinolysis lab samples will be processed at the Children's Hospital of Pittsburgh and assays will be completed within research labs at the University of North Carolina Chapel Hill.

Table 4. Sample Requirements for Laboratory Assessments

Laboratory Test	Blood Volume	Urine Volume
CBC	1-3mL	
Serum Creatinine	1-2mL	
Bilirubin Level	1-2mL	
Urine Pregnancy		5-7mL
Serum Pregnancy	1-2mL	
PT/PTT/INR/Fibrinogen	2-4mL (same tube)	
Urinalysis		5-7mL
Fibrinolysis Labs	5-10mL	

8.9 Bleeding Assessment

Bleeding will be recorded using the WHO Bleeding score as the bleeding assessment tool. Bleeding assessments will be completed by means of a physical assessment of the patient, patient interview and a review of patient chart and laboratory data. Research staff will perform physical assessment and interview prior to reviewing the patient's medical chart and laboratory data to allow an objective assessment. Nursing staff may provide additional details. Bleeding will be classified according to the scale as given below. More detailed assessment of bleeding score by organ system provided in the Appendix.

Table 5. WHO Bleeding Score

Grade 1	Grade 2	Grade 3	Grade 4
Minor Bleeding	Bleeding requiring intervention or treatment (eg nasal packing, bladder irrigation, platelet transfusions or medications to treat bleeding). Grade	Bleeding requiring red blood cell transfusion for treatment or requiring significant intervention to treat bleeding (eg endoscopy)	Bleeding that is fatal or life threatening

	2a: Grade 2 bleeding with the exclusion of skin manifestations		

8.10 Thrombotic Assessment
Assessment for thrombotic event will be performed via a review of medical chart notes and relevant imaging studies obtained within the time period from prior assessment.

9. Adverse Event Reporting
Whenever possible investigators should report adverse events as diseases or syndromes instead of reporting individual components of symptoms, signs, laboratory abnormalities or sequelae.

This study will be using the descriptive terminology developed by the National Cancer Institute for use in reporting adverse events: Common Toxicology Criteria for adverse events (CTCAE) version 4.03. These criteria can be found at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. All Grade 3 or higher adverse events will be documented.

The CTCAE grading scale is applied to each adverse event term. Grades were developed using the following guidelines:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Minimal, local or non-invasive intervention indicated; limiting age-appropriate ADL.
Grade 3: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

The definitions that will be applied to adverse events recorded in this trial are given below:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing

hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

9.1 Frequency of Monitoring

The Investigator will review subject safety data as it is generated. The Investigator and Co-Investigator (Dr. Triulzi) will meet twice monthly to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints and confidentiality of subjects. Additional Co-Investigators and research staff will be invited to attend. Meeting minutes will be made available for all research staff unable to attend. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

9.2 Adverse Event Attribution.

Each adverse event is graded for its attributions to the study to determine whether an adverse event is related to a medical treatment by the following categories:

Table 6. Adverse Event Attribution

Attribution	Description
Not Related	Event clearly related to other factors
Possibly Related	Sequence of events is compatible with study drug, device or procedure but could have been produced by other factors
Probably Related	Sequence of event is compatible with the study drug, device or procedure and

	cannot be explained by other factors without much doubt
Definitely Related	Sequence of event is compatible with the study drug, device or procedure and beyond doubt cannot be explained by other factors

9.3 Adverse Events Reporting Timeline

Life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report.

The FDA will be notified by telephone or facsimile transmission of a human adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written IND Safety Report.

Serious and unexpected adverse events associated with the use of the study drug or procedures will be reported to the IRB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the investigator-sponsor's receipt of the respective adverse event information.

A summary report of the findings will be prepared and submitted to the regulatory agencies.

9.4 Expected Adverse Events

The following information is obtained from the package insert for tranexamic acid.

Tranexamic acid should be reduced in patients with renal insufficiency because of the risk of accumulation. Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with tranexamic acid injection (for this reason patients with visible hematuria will be excluded from the study population). Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving tranexamic acid. Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis. An orthopedic meta-analysis demonstrated no higher risk of venous thromboembolism following hip and knee replacement, surgeries typically thought to be at increased risk of thromboembolism [27]. These findings were supported by a surgical meta-analysis, which found the risk of thromboembolic events with tranexamic acid was uncertain but the risk ratio of events was not increased overall [28]. The CRASH-2 trial utilizing tranexamic acid also found no differences in death from vascular occlusive events [21]. In this study, tranexamic acid will not be administered

concomitantly with Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates, as the risk of thrombosis may be increased.

Tranexamic acid may cause dizziness and therefore may influence the ability to drive or use machines. Convulsions have also been reported, particularly in patients receiving tranexamic acid during cardiovascular surgery and in patients inadvertently given tranexamic acid into the neuroaxial system.

Focal areas of retinal degeneration have developed in cats, dogs, and rats following oral or intravenous tranexamic acid at doses between 250 to 1600 mg/kg/day (6 to 40 times the recommended usual human dose) from 6 days to 1 year. The incidence of such lesions has varied from 25% to 100% of animals treated and was dose-related. At lower doses, some lesions have appeared to be reversible. Limited data in cats and rabbits showed retinal changes in some animals with doses as low as 126 mg/kg/day (only about 3 times the recommended human dose) administered for several days to two weeks. No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials. Tranexamic acid should be discontinued if changes in examination results are found.

An increased incidence of leukemia in male mice receiving tranexamic acid at doses equivalent to as high as 5 g/kg/day may have been related to treatment. Hyperplasia of the biliary tract and cholangioma and adenocarcinoma of the intrahepatic biliary system have been reported in one strain of rats after dietary administration of doses exceeding the maximum tolerated dose for 22 months. Hyperplastic, but not neoplastic, lesions were reported at lower doses. Subsequent long-term dietary administration studies in a different strain of rat, each with an exposure level equal to the maximum level employed in the earlier experiment, have failed to show such hyperplastic / neoplastic changes in the liver. No mutagenic activity has been demonstrated in several in vitro and in vivo test systems.

Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur but disappear when the dosage is reduced. Allergic dermatitis, giddiness, and hypotension have been reported occasionally. Hypotension has been observed when intravenous injection is too rapid. A rare but important potential adverse effect is anaphylactic shock.

9.4.1 Drug Interactions: Avoid Concomitant Use

Avoid concomitant use of Tranexamic Acid with any of the following: Anti-inhibitor Coagulant Complex (Human); Estrogen Derivatives (Contraceptive); Progestins (Contraceptive)

9.4.2 Drug Interactions: Increased/Decreased Effect/Toxicity

Tranexamic Acid may increase the levels/effects of: Anti-inhibitor Coagulant Complex (Human)

The levels/effects of Tranexamic Acid may be increased by: Estrogen Derivatives (Contraceptive); Progestins (Contraceptive); Tretinoin (Systemic)

The levels/effects of Tranexamic Acid may be decreased by: There are no known significant interactions involving a decrease in effect.

10. Loss To Follow-Up

10.1 Death

Due to the severity of underlying disease it is possible that patients may die due to progression of their disease or complications of their treatment prior to completion of treatment with the study drug. It is estimated that fewer than 5% of study patients will die prior to determination of primary and secondary endpoints. In the event that a participant dies prior to completion of the study, data will be included up to the time of their death. Death will be recorded on the end of study form. Additional information to be documented will include the time from consent and attribution of cause of death (due to thrombosis, due to bleeding or due to other causes).

10.2 Study Withdrawal

Subjects are free to stop the study drug at any time. If a patient withdraws their consent for further participation, the subject will be asked to grant consent for the study team to passively monitor their outcomes for major clinical events. For each patient at the end of therapy, the date and time that the study drug is voluntarily stopped will be recorded, along with the reason that the subject so elected. An End of Study form will document whether the subject is:

- Stopping study drug, but will continue to follow all other study-defined procedures and monitoring
- Stopping study drug and study-defined procedures and monitoring but allows investigators to passively monitor their medical record and follow-up for vital status up to 30 days after their last dose of study drug.
- Discontinuing all further contact with study investigators

In order to avoid any doubt, if subjects withdraw consent it will be explained to them that any data obtained up to the point of consent withdrawal will be included in study analysis, regardless of their consent for future monitoring.

The patient's physician or the principal investigator may withdraw the patient from the study for any reason.

10.3 Hospital Discharge

Patients discharged from the hospital within 30 days of activation of the study drug will receive their assigned study drug up until the day of discharge. The day of discharge will be the final day of therapy with the study drug. They will be contacted at 7 days (+/- 3 days) and 30 days (+/- 3 days) post cessation of the study drug. These visits may take place in the outpatient clinic (if coinciding with a regularly scheduled return appointment) or by telephone. During these visits patients will be asked for any bleeding or thrombotic events since study drug cessation.

11. Statistical Considerations and Analysis

11.1 Statistical Hypothesis

The hypothesis is that tranexamic acid can be safely added to standard care regimens in patients with hematologic malignancies or solid tumors during periods of severe thrombocytopenia and that the study dose of tranexamic acid will sufficiently suppress fibrinolysis

11.1.1 Primary Endpoints

- Assessment of feasibility of recruitment by monitoring number of patients screened, number of patients eligible for enrollment and rate of recruitment (both start-up and ongoing) during study period
- Assessment of safety of tranexamic acid in this population by reported adverse events, serious adverse events and death.
- Assessment of the suppression of fibrinolysis by tranexamic acid will consider the difference in fibrinolytic activity in blood samples obtained from participants at the start of the study prior to receipt of the study drug and after achieving steady state.

11.1.2 Secondary Endpoints

- Assessment of the effect of tranexamic acid on bleeding will consider the difference in the proportion of patients experiencing WHO Grade 2 or higher bleeding between the two study arms following activation of the study drug and until study drug cessation, the proportion of patients with any grade bleeding event following activation of study drug, the highest grade of bleeding experienced during study period and the length of time from study drug activation to WHO Grade 2 or higher bleeding event
- Assessment of the effect of tranexamic acid on platelet transfusion requirement will consider the difference in the number of platelet transfusions administered per patient between the study arms following activation of the study drug and until study drug cessation.

11.2 Randomization

Patients will be randomized by the investigational pharmacy staff to receipt of either tranexamic acid or placebo (normal saline) in a 1:1 fashion. Randomization will be further balanced within blocks of size four. Patients will not be stratified by disease group owing to the small sample size.

11.3 Analysis Populations

Participants will be analyzed according to the groups to which they were initially randomized: tranexamic acid or placebo. All efficacy analysis will be by an Intent to Treat strategy. Participants will be included in the analysis if they received one or more dose of the study drug, even if participant discontinued participation, cross over between treatment groups or received prophylactic transfusions at a threshold higher than that prescribed in the protocol.

Efficacy analysis on patients will include data gathered on patients from the time of activation of the study drug until discharge or until a point 30 days following activation of the study drug, which ever time point occurs sooner. Any participants who have been consented to participate within the study and randomized to a treatment group but did not meet criteria to begin treatment with the study drug (whether due to development of

exclusion criteria or due to platelet count remaining >30,000/uL) and did not receive any doses of the study drug will not be included in the efficacy analysis.

The population of patients used for analysis of safety will be all patients who receive one of more dose of the study drug. Follow-up for mortality and for thrombotic events will occur at 7 days (+/- 3 days) and 30 days (+/- 3 days) post activation. Adverse events and Serious Adverse events will be based on clinical diagnosis obtained from review of the medical record and by patient report during the surveillance period. Patients will be assessed by daily visits and medical chart reviews by the investigator or study staff during the study period. Patients will be assessed by in-hospital visit (if in patient), clinic visit or telephone (if outpatient) during follow-up period after cessation of the study drug.

11.4 Competing Risks

11.4.1 Death

Due to the severity of underlying disease it is possible that patients may die from progression of their disease or complications of their treatment prior to completion of treatment with the study drug. It is estimated that fewer than 5% of study patients will die prior to determination of primary and secondary endpoints. In the event that a participant dies prior to completion of the study data will be included up to the time of their death. No further assumptions will be made regarding future bleeding rates in this population

11.4.2 Hospital Discharge

Patients discharged from the hospital within 30 days of activation of the study drug will receive their assigned study drug up until the day of discharge. The day of discharge will be the final day of therapy with the study drug. They will be contacted at 7 days (+/- 3 days) and 30 days (+/- 3 days) post cessation of the study drug. These visits may take place in the outpatient clinic (if coinciding with a regularly scheduled return appointment) or by telephone. During these visits patients will be asked for any bleeding or thrombotic events since study drug cessation.

11.5 Statistical Analysis Planned

All statistical comparisons will be based on a two-sided model using a 0.05 level of significance and two-sided 95% confidence intervals.

Data on the number of patients screened, the number of patients eligible for study inclusion, the number of eligible patients who consent to study inclusion and the number of consented patients activated to the study drug will be organized in CONSORT diagram. Run chart may also be used to demonstrate study momentum over time period of study enrollment in graphical form. Suppression of fibrinolysis will be analyzed by matched pair analysis using a T-test of means.

For secondary endpoints, events of WHO Grade 2 or higher bleeding will be compared through the use of odds ratio or T-test statistic of means. The mean number of platelet transfusions will be analyzed using a T-test statistic of means.

Patients will be followed for all clinical outcomes regardless of adherence to the prescribed regimen for the study drug.

Additional statistical analysis will be considered at the time of trial completion based on the data obtained.

11.6 Sequential Stopping Rules

When 50% of target sample has been recruited (10 patients) an independent Data and Safety Monitoring board will conduct an interim analysis to monitor study progress, integrity, and patient safety (by review of incidence of adverse events and serious adverse events). The exact stopping rule will be chosen in discussion with the DSMB prior to the interim analysis. There will be no early stopping boundary for efficacy of tranexamic acid over placebo.

11.7 Sample size

The goal of this study is to recruit a total of 20 participants in order to demonstrate study feasibility. Study goal is to recruit patients at a rate of 1- 2 participants per month. Our estimate is that for every two patients eligible for study inclusion and approached for trial enrollment there will be one patient who will sign consent for study enrollment. This study will not be adequately powered to detect a significant reduction in bleeding rates. However, the goal is to establish safety of tranexamic acid and ability to conduct a larger trial of efficacy in the future. Results of this trial, including recruitment rate, will allow for calculations as to the ideal sample size, ideal number of trial sites and the ideal length of study period for future trials.

If accrual to the study does not meet expectation then study inclusion criteria will be reviewed to consider including patients with additional diagnosis and/or platelet transfusion thresholds.

12. Risks Management Procedures

12.1 Protection Against Risks

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

All demographic and clinical information about the subject will be stored on a Case Report Form which will be completed for each subject enrolled into the clinical study. The Investigator will review, approve and sign/date each completed CRF; the Investigator's signature serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The data will be stripped of individual identifiers and stored anonymously on CRF with a unique study subject ID. No personal identifier will be used in any publication or communication used to support this research study. The study subject ID code will be

used in the event it becomes necessary to identify data specific to a single subject. Representatives from the IRB and FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human study subjects in clinical research. All medical and research records will be de-identified prior to being photocopied. Study results will not be given to individual subjects but will be published in the open literature and made available as a matter of public record. Data forms will be held securely in a locked file at the desk of one of the primary investigator at the trial site.

Information linking subject identifiers with the coded subject number will be stored in a password protected document on the UPMC Secure OneDrive network and accessed using the UPMC network. Screening log documenting a list of all patients screened for eligibility will be stored on a password-protected document on the UPMC secure OneDrive network and accessed using the UPMC network. These documents will destroyed upon completion of study enrollment and data collection. Access to data will be limited to the Investigators and study staff under the supervision of the Investigators.

Blood specimens collected for fibrinolysis labs will be stripped of subject identifiers and labelled according to a similar coding protocol as described above. Blood specimens shipped to UNC research labs for fibrinolysis assays will not contain any identifying information. Remaining specimens will be disposed of following completion of assays. Blood specimens maintained at the Children's Hospital of Pittsburgh of UPMC will be labelled according to a similar coding protocol as described above. They will be stored indefinitely unless requested otherwise in writing with patient and used for later assays of biomarkers of fibrinolysis.

All staff involved in this study are properly credentialed and instructed in the areas of testing, confidentiality, and safety.

The Investigator will retain the data for the entire period of this study and will retain the specified records and reports for up to two years after investigations under the IND have been discontinued and the FDA so notified. The Investigator may continue to use and disclose subjects' de-identified information for the purpose of this study for a minimum of seven years after final reporting or publication of the study. If the subject and/or legal representative decide to withdraw or be withdrawn from study participation, they may request that the study data and samples be destroyed. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

12.2 Data Monitoring and Interim Analysis

Study monitoring will be the responsibility of the Principal Investigator. The investigator will maintain regular correspondence with study staff and monitor compliance with the investigation plan and relevant regulations and maintenance of complete records.

A Data Monitoring and Safety Board (DMSB) has been established. The DMSB is independent of the study organizers and will consist of three individuals with expertise in

the field of Hematology/Oncology, Bone Marrow Transplantation and Transfusion Medicine. The DSMB will meet after enrollment of the first 10 patients and at the conclusion of the trial to review study progress (including patient recruitment and protocol adherence) as well as safety data (Serious adverse events, adverse events, bleeding events and mortality). More frequent meetings may be requested by the DSMB if necessary for adequate review of safety. During the period of recruitment to the study, interim data will be supplied, in strict confidence, to the DMSB along with any other data the committee may request.

The Adverse Event Reports will be included in the reports. The DSMB will have access to all data. Data will be provided in aggregate with both arms combined and also disaggregated by arms A and B without revealing the identity of the arms. Should DSMB findings require breaking of the study blind, then unblinded data will be provided. In light of these interim analyses the DMSB will advise the study investigators on its view:

- The trial be stopped for reasons of patient safety
- The protocol be better modified to protect patient safety

Unless one of these events were to occur the investigators will remain ignorant of interim results.

A copy of the DMSB findings and recommendation will be submitted to the local IRB.

13. Records and Documentation

13.1 Data Management

Data will be collected in the manner described below. This study will use a paper based data collection system.

Case Report Forms (CRFs). Case report forms will be used to collect all subject study data during the course of the study. All protocol deviations will be documented and a justification for any missed assessments will be provided on the protocol deviation log. Completion of the CRFs will be on paper forms. All paper forms once completed will remain in a locked filing cabinet at the desk of the primary investigator. Any internal study team communications regarding the documentation of information on case report forms will be resolved via the secure UPMC email or phone communication and corrections will be made to appropriate CRFs. Any corrections to case report forms will be documented accordingly. The Investigator will allow the FDA, or other regulatory bodies to review the study files, subject CRFs, medical records and other study-related documents. Access to data will be limited to those who need access to perform their tasks.

Serious Adverse Events.
The Unexpected/Serious Adverse Event Form must be completed within 48 hours by the primary investigator, with appropriate attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate and sign the

form.

Information about the following events will be collected and assessed:

- Serious adverse events, regardless of attributed relationship to study drug, that occur after study drug is activated
- Any unexpected adverse events (all grades), attributed as possible, probably or definitely related to the study drug.
- Causality of all serious adverse events

Follow-up: Following a Serious Adverse Event subjects must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilized. Follow-up should continue after completion of the study period if necessary. Follow up information may be provided on a separate form provided once a SAE report form has been received. The subject must be identified by trial number only, the subject's name will not be used on any correspondence.

14. Institutional Review Board (IRB)

The Investigator will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation. The Investigator should also notify the sponsor of this event.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Investigator's decision to modify the previously accepted clinical protocol:

- for a Phase 1 clinical study: The Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be addressed in the Annual Report to the IND.

- for Phase 2 and 3 clinical studies: The Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 or Phase 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 and 3 clinical protocol changes requiring the submission of a Protocol Amendment include:
    - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
    - Any significant change in the design of the protocol (such as the addition or deletion of a control group)
    - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

15. Trial Committees

15.1 Data and Safety Monitoring Board (DSMD)

The trial conduct and patient safety will be evaluated and monitored by an independent DSMB. Membership will be composed of three members, with representative from the division of Hematology, Bone Marrow Transplantation and Transfusion Medicine. All members will be independent of study investigators and have no financial or intellectual conflicts of interest. The DSMB will meet after enrollment of the first 10 patients and at the conclusion of the trial to review study progress (including patient recruitment and protocol adherence) as well as safety data (Serious adverse events, adverse events, bleeding events and mortality). More frequent meetings may be requested by the DSMB if necessary for adequate review of safety.

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