NCT02578901

A-TREAT Protocol Version 3.5

2018-05-07

American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT)

A randomized, controlled trial evaluating the safety and efficacy of tranexamic acid in patients with hematologic malignancies and severe thrombocytopenia

Version 2.0	23 September 2015	FDA IND Initial Submission
Version 2.1	16 October 2015	FDA IND Amendment 1
Version 2.2	21 October 2015	FDA IND Amendment 2
	FDA IND 128032 approval 2015-10-23	
Version 2.3	6 January 2016	
Version 2.4	3 February 2016	FDA IND Amendment 3
Version 2.5	7 March 2016	
Version 3.0	9 May 2016	DSMB Approved Version
Version 3.1	13 June 2016	FDA IND Amendment 4
Version 3.2	20 April 2017	FDA IND Amendment 5
Version 3.3	26 June 2017	FDA IND Amendment 6
Version 3.4	12 December 2017	FDA IND Amendment 7
Version 3.5	07 May 2018	FDA IND Amendment 8

Approved by:

Name: Role: Principal Investigator(s)

Signature: Date:

Authorized by:

Name: Role: DCC Principal Investigator

Signature: Date:

GENERAL INFORMATION

This document provides in depth background information for the A-TREAT trial. It also serves as a guidance document for the proper identification, treatment and maintenance of A-TREAT trial patients. This protocol should not be used as a guide for the treatment of patients not enrolled in the A-TREAT clinical trial. Every care was taken in its drafting, but corrections or amendments may be necessary; these will be circulated to registered investigators in the trial, but centers entering patients for the first time are advised to contact the Data Coordinating Center (DCC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Principal Investigator.

Contacts
If you have any queries regarding this protocol, or the general conduct of the trial, please contact one of the following people:

Principal Investigators
- Terry Gernsheimer, MD (University of Washington, Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center)
- Susanne May, PhD (University of Washington)
- Darrell Triulzi, MD (University of Pittsburgh)
- Nigel Key, MD (University of North Carolina)
- Sherrill Slichter, MD (Bloodworks Northwest)

Trial email: help@A-TREAT.org

Compliance Statement
The study will be conducted according to the protocol and in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP), Belmont Principles, and other applicable regulatory requirements. All identified study personnel will be trained to perform their roles and will carry out their responsibilities in accordance with ICH GCP guideline and clinic site SOPs.

Funding Sources: National Heart, Lung and Blood Institute of the National Institute of Health
Data Coordinating Center: Susanne May, PhD (University of Washington)

Clinical Coordinating Center: University of Washington

Lead Trial Statistician(s): Susanne May, PhD

Trial Sites IRBs of Record:
- University of Washington IRB
- University of Pittsburgh IRB
- University of North Carolina IRB

PROTOCOL SYNOPSIS

Despite major advances in optimizing platelet transfusion therapy, bleeding remains a problem in patients with thrombocytopenia due to chemotherapy induced marrow aplasia and hematopoietic stem cell disorders.[1] Baseline level of bleeding does not appear to be affected by increasing the platelet transfusion threshold[2,3] and does not appear to be dependent on the platelet count when it is above 5,000/μl. In the PLADO (Platelet Dose) Trial of 1272 patients, WHO grade 2 bleeding occurred in approximately 70% of all subjects regardless of platelet dose transfused prophylactically for patients with platelet counts of ≤10,000/μL[4]. Withholding transfusion may lead to serious and fatal bleeding[5]. In a 600 patient trial of therapeutic vs. prophylactic platelet transfusion (TOPPS)[6], bleeding remained a common event. Maintenance of a safe platelet count may be difficult due to shortened platelet survival in severely thrombocytopenic and critically ill patients.[7] Patients who are refractory to platelet transfusion may require expensive and difficult to obtain matched platelets to prevent serious bleeding. Maintenance of the platelet count above a prescribed trigger in outpatients can require daily laboratory work and frequent visits to the clinic for transfusions.

Epsilon Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) are inhibitors of fibrinolysis that can be given either intravenously or orally. Inhibitors of fibrinolysis have been used for many years to prevent and treat bleeding due to fibrinolysis intra- and postoperatively[8] and have been shown to be useful in in patients with platelet function and coagulation defects such as hemophilia[9]. Reports of the use of these agents to prevent or treat bleeding in thrombocytopenic patients have been encouraging[10,11,12] and suggest that in many patients bleeding can be prevented or stopped. Such anecdotal, retrospective single center reports lead many physicians to prescribe EACA or TXA to prevent or treat bleeding in thrombocytopenic patients refractory to platelet transfusions; however, lack of evidence of efficacy and safety prevent its use from becoming standard of care.

The results of this study will change practice by providing evidence as to whether or not the fibrinolytic agent TXA is an effective and safe treatment when used as an adjunct to platelet transfusion therapy to prevent bleeding in patients with hypoproliferative thrombocytopenia. A safe treatment to decrease bleeding and transfusion requirements in these patients would greatly improve patient outcomes and quality of life, and have a major health economic impact.

Objectives

The purpose of this study is to compare the incidences of bleeding and thrombosis, and the transfusion requirements in patients randomized to receive TXA or a placebo for hypoproliferative thrombocytopenia secondary to primary marrow disorders, chemotherapy, immunotherapy, radiation and/or hematopoietic stem cell transplant.

Study Design

Double blind, randomized, placebo controlled trial. Subjects will be screened for eligibility by trained study staff after being identified by primary providers as likely to have platelet counts of ≤10,000/μl for ≥5 days. Bleeding and thrombotic assessments will be performed daily on inpatient subjects via chart review, subject interview and physical examination. Outpatient subjects will maintain a daily diary and be seen at least weekly in clinic.

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ABBREVIATIONS AND GLOSSARY

ADL	Activities of Daily Living
AE	Adverse Event
AR	Adverse Reaction
CF	Consent Form
CRF	Case Report Form
CTCAE	Common Toxicology Criteria for Adverse Events
D5W	5% Dextrose in Water
DCC	Data Coordinating Center
DCF	Data Clarification Form
DDAVP	Desmopressin Acetate
DIC	Disseminated Intravascular Coagulation
DSMB	Data and Safety Monitoring Board
EACA	Epsilon Aminocaproic Acid
DMS	Data Management System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hour
HIV	Human Immunodeficiency Virus
HTLV	Human T-lymphotropic Virus
HUS	Hemolytic Uremic Syndrome
IB	Investigator's Brochure
IRB	Institutional Review Board
ISRCTN	International Standard Randomized Controlled Trial Number
ITP	Immune Thrombocytopenia
IV	Intravenous
LAR	Legally Authorized Representative
NHLBI	National Heart, Lung and Blood Institute
PCC	Prothrombin Complex Concentrate
PI	Principal Investigator
PIS	Patient Information Sheet
PO	Oral
Q	Every
RCT	Randomized Controlled Trial
RN	Registered Nurse
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOC	Standard of Care
SCT	Stem Cell Transplant
SOP	Standard Operating Procedure
SOS	Sinusoidal Obstructive Syndrome
SSA	Site Specific Assessment
Study Drug	Tranexamic Acid or matching placebo
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TTP	Thrombotic Thrombocytopenic Purpura
TXA	Tranexamic Acid
UAR	Unexpected Adverse Reaction
VOD	Veno-occlusive Disease
VTE	Venous Thromboembolism
WBC	White Blood Cell
WBD	Whole Blood Derived
WHO	World Health Organization

1. SUMMARY

Name of Sponsors:
National Heart, Lung and Blood Institute, National Institutes of Health

Name of Investigational Products:
Tranexamic Acid (TXA)

Name of Active Ingredient:
Tranexamic Acid

Title of Study:
A-TREAT: American Trial Using Tranexamic Acid in Thrombocytopenia

Study Centers:
University of Washington (UW)
University of North Carolina (UNC)
University of Pittsburgh (UP)

Principal Investigators:
Terry Gernsheimer, MD (University of Washington)
Sherrill J. Slichter, MD (Bloodworks Northwest)
Nigel Key, MD (University of North Carolina)
Darrell Triulzi, MD (University of Pittsburgh)
Susanne May, PhD (University of Washington)

Studied Period (4 years):	**Phase of development:** Phase 3
Estimated date first subject enrolled: Q1 2016 Estimated date last subject completed: Q4 2019	

Objectives:
The purpose of this study is to conduct a prospective, randomized, blinded, placebo controlled trial to evaluate the usefulness of antifibrinolytic therapy with tranexamic acid in preventing bleeding in patients who are thrombocytopenic due to primary bone marrow disorders or chemotherapy, immunotherapy, and/or radiation therapy. The results of this study will change practice by providing evidence as to whether or not TXA is effective and safe treatment when used as an adjunct to platelet transfusion therapy in the thrombocytopenic patient.

Primary Objectives:

- Assess whether TXA reduces bleeding in patients with thrombocytopenia due to aplasia, chemotherapy, stem cell transplantation for hematologic disorders.
- Obtain data on the safety of TXA in thrombocytopenic patients.
- Assess whether TXA therapy can reduce the number of prophylactic platelet transfusions in thrombocytopenic patients undergoing treatment with chemotherapy or stem cell transplantation.

Secondary Objectives:

- To examine AEs, and clinical laboratory parameters related to treatment with TXA.
- To examine platelet efficacy endpoints in vivo including spontaneous bleeding rates, platelet count increments (CI), and corrected count increments (CCI).

Methodology:
Randomized, double-blind, placebo controlled, superiority trial enrolling thrombocytopenic adult patients with aplasia or hematologic malignancies receiving intensive chemotherapy, radiation, and/or

hematopoietic stem cell transplantation. Subjects will be randomized in a 1:1 ratio to either the antifibrinolytic TXA or placebo (oral or intravenous [IV]) treatment arms when their platelet count falls below 50,000/μl, and is expected by their primary provider to have platelet counts of ≤10,000/μl for ≥5 days. When a randomized subject's platelet count falls to < 30,000/μl, the subject will be activated to begin their assigned study drug. Treatment with the study drug will continue until the platelet count is ≥ 30,000/μl for 46 hours without platelet transfusion support, until a maximum of 30 days after treatment activation, or until the subject meets other protocol specified safety criteria for stopping study drug, whichever comes first. Data collection for primary efficacy endpoints will continue for 30 days after activation of study drug, with additional long term follow-up at 14 and 30 days and 120 days post activation of study drug. A bleeding assessment form will be completed daily by a trained member of the research staff for each day a subject is hospitalized. Outpatient subjects (including inpatient subjects that are discharged home prior to completion of the trial follow-up period) will complete a daily Self-Assessment Bleeding Diary and a trained member of the research staff will review the subject's diary, records of all clinic visits for transfusions, bleeding and adverse events at least once a week. Adverse event data will be collected for 30 days after receipt of last dose of study drug.

Estimated Number of Subjects Screened: Approximately 2,500 subjects screened

Maximum Number of Subjects Enrolled: Approximately 360 subjects will be enrolled at 3 U.S. study sites to obtain 330 activated subjects.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion criteria (all must be met):

- Must be ≥ 18 years of age
- Confirmed diagnosis of a hematologic malignancy or aplasia
- Undergoing or planned chemotherapy, immunotherapy, or hematopoietic stem cell transplantation
- Anticipated to have hypoproliferative thrombocytopenia resulting in a platelet count of ≤ 10,000/μl for ≥ 5 days
- Able to provide informed consent and comply with treatment and monitoring, or having a Legally Authorized Representative (LAR)

Exclusion criteria (none can be present):

- Diagnosis of acute promyelocytic leukemia undergoing induction chemotherapy
- History of ITP, TTP or HUS
- Subjects receiving L-asparaginase as part of their current cycle of treatment
- Subjects with a past history or current diagnosis of arterial or venous thromboembolic disease including acute coronary syndrome, peripheral vascular disease and retinal arterial or venous thrombosis (except when a prior history of central line thrombosis has resolved)
- Subjects with a diagnosis/previous history of sinusoidal obstruction syndrome (also called veno-occlusive disease)
- Subjects receiving any pro-coagulant agents (e.g. DDAVP, recombinant Factor VIIa or Prothrombin Complex Concentrates (PCC) and/or an antifibrinolytic agent within 48 hours of enrollment, or with known hypercoagulable state
- Known inherited or acquired bleeding disorder including, but not limited to:
    - Acquired storage pool deficiency
    - Paraproteinemia with platelet inhibition
- Known inherited or acquired prothrombotic disorders, including antiphospholipid syndrome. Those with lupus anticoagulant or positive antiphospholipid serology without thrombosis are not excluded.
- Subjects receiving anticoagulant therapy or anti-platelet therapy (except when receiving prophylactic anticoagulant or low dose aspirin therapy for prophylaxis only with a plan to discontinue when the platelet count falls below 50,000)
- Patients with DIC according to the patient's physician
- Subjects with WHO Grade 2 bleeding or greater within 48 hours prior to activation
- Subjects requiring a platelet transfusion threshold > 10,000/μl at time of randomization
- Subjects with anuria (defined as urine output < 10mls/hr over 24 hours)
- Subjects on dialysis
- Subjects with creatinine ≥5.7mg/dL

- Subjects who are pregnant or nursing or unwilling to use contraception during and for 30 days after taking the study drug (both males and females)
- Subjects enrolled in other trials involving platelet transfusions, anti-fibrinolytics, platelet growth factors or other pro-coagulant agents.
- Known allergy to tranexamic acid
- Having been previously randomized in this study at any stage of their treatment
- Subjects who are unwilling to accept blood or blood component transfusions

Drug Dosage, Schedule, and Mode of Administration:

Inpatient subjects will receive TXA or placebo via oral (PO) or intravenous (IV) administration- the decision concerning route of administration will be left to the discretion and documentation of the treating investigator or treating physician. Outpatient subjects will receive TXA or placebo via oral administration.

Dosing Schedule: TXA, 1.0g IV or 1.3g PO every 8 hours versus a placebo equivalent every 8 hours (oral study drug supplied by a contracted investigational pharmaceutical company).

Duration of Treatment:

Subjects will receive study drug for up to 30 days per methodology referenced above and study specific follow-up will occur at 14 (+ 7 day window), 30 days post discontinuation of study drug and 120 days post activation of study drug. Adverse events will be followed for 30 days after the last dose of study drug is taken.

Criteria for Evaluation:

Primary Efficacy Endpoints:

- Proportion of patients with bleeding of WHO grade 2 or above, over the study period of 30 days after activation of study drug.

Secondary Efficacy Endpoint:

- Number of platelet transfusions per patient during the first 30 days post activation of study drug
- Number of days alive and without WHO grade 2 bleeding or greater during the first 30 days after activation of study drug

Supportive and Exploratory Efficacy Endpoints:

Alternative measures of bleeding

- Number of days with bleeding/thrombocytopenia during the first 30 days post activation of study drug
- Time from activation of study drug to first episode of bleeding of WHO grade 2 or greater or death, whichever comes first within the first 30 days post activation of study drug
- Highest grade of bleeding a patient experiences during the first 30 days post activation of study drug
- Death ascribed to bleeding during the first 30 days post activation of study drug

Alternative measures of transfusion frequency

- Number of platelet transfusions/patient by thrombocytopenic day during the first 30 days post activation of study drug
- Number of red cell transfusions/patient and by thrombocytopenic day during the first 30 days post activation of study drug
- Proportion of patients surviving at least 30 days post activation of study drug without a platelet transfusion
- Proportion of patients surviving at least 30 days post activation of study drug without a red cell transfusion
- Number of patients with platelet count nadir > 10,000/μl over the study period of 30 days from activation of study drug

Safety Endpoints:

- Incidence of thrombotic events from first day on study drug up to and including 120 days after activation of study drug.
- Incidence of veno-occlusive Disease (VOD; sinusoidal obstructive syndrome, SOS) from the first day on study drug up to and including 30 days of last receipt of study drug
- All-cause mortality during the first 30 days and the first 120 days post activation of study drug
- Death ascribed to thrombosis during the first 120 days post activation of study drug

- Incidence of adverse events (AEs) and serious adverse events (SAEs) categorized by CTCAE v4.0 from the first day on study drug up to and including 30 days after the last dose of study drug is received

Sub-Group Analysis:

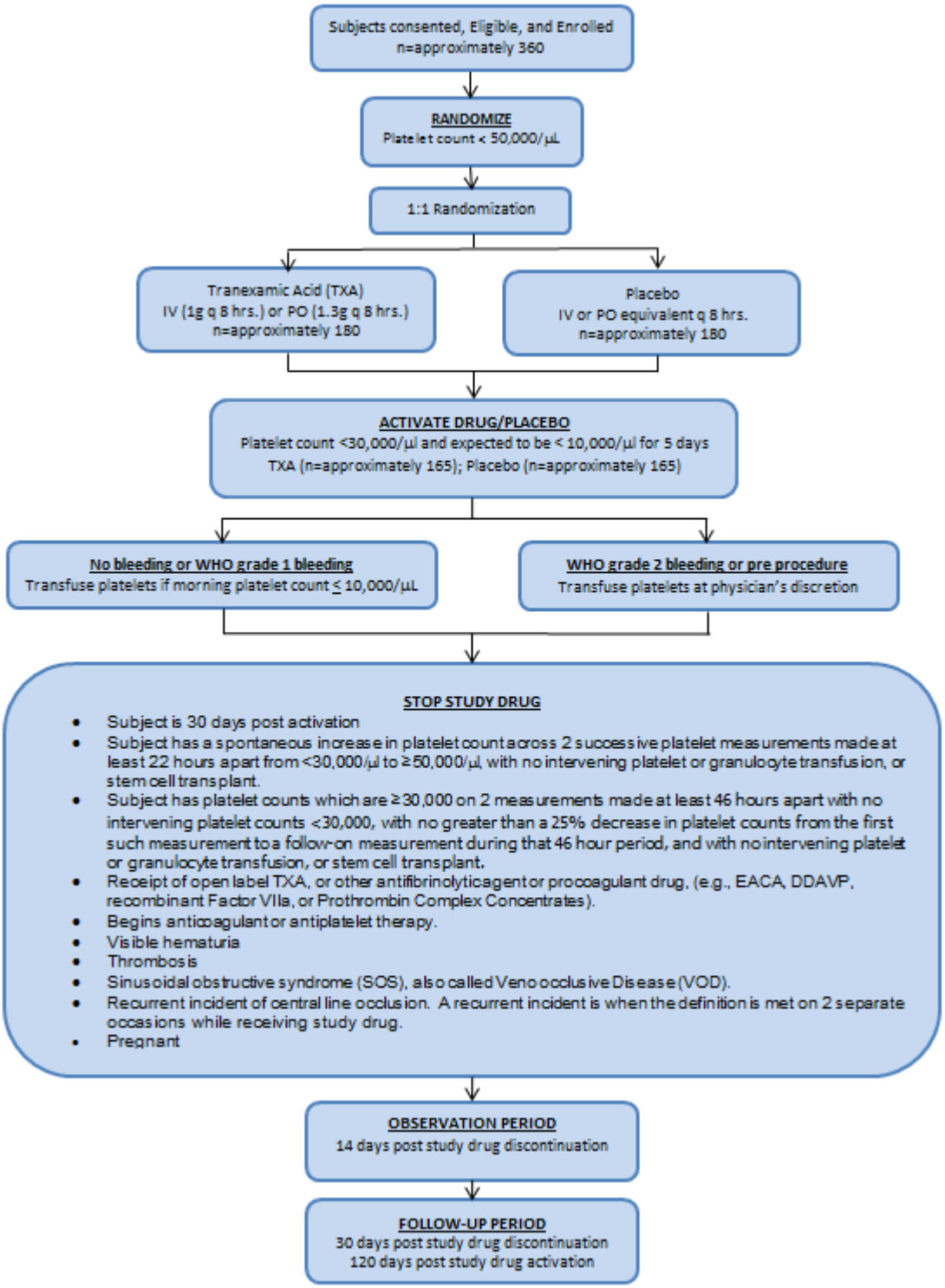
- WHO grade 2 or above bleeding will be assessed separately among patients who did and did not have bleeding at randomization, as well as within each of the disease groups of allogeneic transplant, autologous transplant, and leukemia.

Statistical Methods and Sample Size:

The odds of bleeding at WHO grade 2 level or above will be analyzed in a logistic regression model adjusting for treatment arm, clinical site as a factored variable, and disease group (allogeneic transplant, autologous transplant, or leukemia) as a factored variable. The test statistic will be based on the score statistic for the treatment arm parameter from the logistic regression model with adjustment for multiply imputed missing data.

Calculation of sample size and statistical power were based on the chi-squared test of association, which is equivalent to the score test from simple logistic regression. Based on 1:1 randomization, a one-sided level of significance 0.025, a design alternative hypothesis of 30% relative reduction in bleeding rates (57% on the placebo arm and 40% on TXA), a sample size of 330 subjects (165 TXA, 165 placebo) will provide 88% statistical power to declare statistical significance on the primary endpoint. This sample size will provide 74.8% statistical power to detect a 25% relative reduction in bleeding rates (57% vs 42.75%). With the planned sample size and a placebo bleeding rate of 57%, an observed absolute decrease in WHO grade 2 or above bleeding of 10.6% (so 57% on placebo, 46.4% on TXA) would be judged statistically significant.

Figure 1. Trial Entry, Randomization, Treatment, and Monitoring Flow Diagram



2. BACKGROUND

Despite major advances in optimizing platelet transfusion therapy, bleeding remains a problem in patients with thrombocytopenia due to chemotherapy induced marrow aplasia and primary hematopoietic stem cell disorders[1]. Baseline level of bleeding does not appear to be affected by increasing the platelet transfusion threshold[2,3], and does not appear to be dependent on the platelet count when it is above 5,000/µl. In the PLADO (Platelet Dose) Trial of 1272 patients, WHO grade 2 bleeding occurred in approximately 70% of all subjects regardless of platelet dose transfused prophylactically for patients with platelet counts of ≤10,000/µL[4]. Similarly in a 600 patient trial of therapeutic vs. prophylactic platelet transfusion (TOPPS)[6],

bleeding remained a common event. Withholding transfusion may lead to serious and fatal bleeding[5].

Maintenance of the platelet count in a safe range may be difficult due to severe shortening of the platelet survival in severely thrombocytopenic and critically ill patients[7] and patients who are refractory to platelet transfusion therapy may require specially matched platelets that are difficult and expensive to obtain. In the outpatient setting, maintenance of the platelet count above a prescribed trigger may require almost daily laboratory work and frequent transfusions.

Platelet transfusions are a limited and expensive resource, and demand for these products is rising in many countries. The increasing demand for platelet transfusions in the US raises concerns of future shortages. Hematology/Oncology patients are transfused more platelets than any other hospital service (31%)[13]. Any treatment that could reduce reliance on platelet transfusion support would have major cost-saving implications.

Other means that have been used to decrease bleeding incidence include maintenance of higher hematocrits to improve platelet function[14] and the use of pharmacologic agents to improve platelet function[15,16]. Epsilon Aminocaproic Acid (EACA) and Tranexamic Acid (TXA) are inhibitors of fibrinolysis that can be given either intravenously or orally. Inhibitors of fibrinolysis have been used for many years to prevent and treat bleeding due to fibrinolysis intra- and postoperatively[8]. These drugs have also been shown to be useful in patients with platelet function and coagulation defects such as hemophilia[17]. Reports of the use of these agents to prevent or treat bleeding in thrombocytopenic patients have been encouraging[9,10,11,12] and suggest that in many patients bleeding can be prevented or stopped with the use of these agents. However, the reports of success have been anecdotal and retrospective reviews of single institution experiences. Currently many physicians administer antifibrinolytic agents to treat bleeding in thrombocytopenic patients or to prevent bleeding in the thrombocytopenic patient refractory to platelet transfusions. Due to the lack of evidence of its efficacy and safety, the treatment has not become standard of care. A pivotal study of antifibrinolytic therapy will improve patient care by leading physicians to either adopt it as an effective and safe treatment for the prevention of thrombocytopenic bleeding, or to abandon its use for this purpose.

The purpose of this study is to conduct a prospective, randomized, blinded, placebo controlled trial to evaluate the usefulness of an antifibrinolytic therapy, TXA, in preventing bleeding in patients who are thrombocytopenic due to primary bone marrow disorders or chemotherapy, immunotherapy and/or radiation therapy. The results of this study will change practice by providing evidence as to whether or not TXA is an effective and safe treatment when used as an adjunct to platelet transfusion therapy in the thrombocytopenic patient.

3. ENDPOINTS

3.1 PRIMARY ENDPOINT

Proportion of patients with bleeding of WHO grade 2 or above during the first 30 days after activation of study drug (appendix 2).

3.2 Secondary Endpoints

- Number of platelet transfusions per patient during the first 30 days post activation of study drug
- Number of days alive and without WHO grade 2 bleeding or greater during the first 30 days post activation of study drug

3.3 Supportive and Exploratory Efficacy Endpoints

3.3.1 Alternative measures of bleeding:

- Number of days with bleeding/thrombocytopenia during the first 30 days post activation of study drug

- Time from activation of study drug to first episode of bleeding of WHO grade 2 or greater or death, whichever comes first
- Highest grade of bleeding a patient experiences during the first 30 days post activation of study drug
- Death ascribed to bleeding during the first 30 days post activation of study drug

3.3.2 Alternative Measure of Transfusion Frequency:

- Number of platelet transfusions/patient by thrombocytopenic day during the first 30 days post activation of study drug.
- Number of red cell transfusions/patient and by thrombocytopenic day during the first 30 days post activation of study drug.
- Proportion of patients surviving at least 30 days post activation of study drug without a platelet transfusion.
- Proportion of patients surviving at least 30 days post activation of study drug without a red cell transfusion.
- Number of patients with platelet count nadir > 10,000/μl over the study period of 30 days from activation of study drug.

3.4 Safety Endpoints

The incidence of serious adverse events (SAEs) and adverse events (AEs) will be collected from the time of consent, up to and including 30 days after the last dose of study drug, categorized using CTCAE v4.0 criteria, and compared across treatment arms. In addition, the following protocol defined safety endpoints will be collected:

- Incidence of thrombotic events from first day on study drug up to and including 120 days after activation of study drug. Thrombotic event is defined by the presence of a venous or arterial clot demonstrated by positive diagnostic imaging, which can include Doppler/ultrasound, CT and MRI, and interpretation by a local radiologist who will be blinded to the study assignment and unlikely to know patient is on a study. Acute coronary syndrome will be made on the basis of enzyme and EKG abnormalities consistent with that diagnosis and interpreted by the attending physician or consulting cardiologist as such.
- Incidence of veno-occlusive Disease (VOD; sinusoidal obstructive syndrome, SOS) from the first day on study drug up to and including 30 days after last dose of study drug.
- All-cause mortality during the first 30 days and the first 120 days post activation of study drug.
- Death ascribed to thrombosis during the first 120 days post activation of study drug.

3.5 Sub-group Analyses

WHO grade 2 or above bleeding will be assessed separately among patients who did and did not have bleeding at randomization, as well as within each of the disease groups of allogeneic transplant, autologous transplant and leukemia.

4. TARGET PATIENT POPULATIONS

Patients with hematologic malignancies receiving intensive chemotherapy and/or stem cell transplantation.

4.1 Inclusion Criteria (all must be met)

4.1.1 ≥18 years of age

4.1.2 Confirmed diagnosis of a hematological malignancy or aplasia

4.1.3 Undergoing or planned chemotherapy, immunotherapy, or hematopoietic stem cell transplantation

4.1.4 Anticipated to have hypoproliferative thrombocytopenia resulting in a platelet count of ≤ 10,000/μl for ≥ 5 days

4.1.5 Able to provide informed consent and comply with treatment and monitoring or having a Legally Authorized Representative (LAR)

4.2 Exclusion Criteria (none can be present)

- **4.2.1** Diagnosis of acute promyelocytic leukemia undergoing induction chemotherapy
- **4.2.2** History of ITP, TTP or HUS
- **4.2.3** Subjects receiving L-asparaginase as part of their current cycle of treatment
- **4.2.4** Subjects with a past history or current diagnosis of arterial or venous thromboembolic disease including, acute coronary syndrome peripheral vascular disease and retinal arterial or venous thrombosis (except when a prior history of central line thrombosis has resolved)
- **4.2.5** Subjects with a diagnosis/previous history of veno-occlusive disease (also called sinusoidal obstruction syndrome)
- **4.2.6** Subjects receiving any pro-coagulant agents (e.g. DDAVP, recombinant Factor VIIa or Prothrombin Complex Concentrates (PCC)) and/or an antifibrinolytic agent within 48 hours of enrollment, or with known hypercoagulable state
- **4.2.7** Known inherited or acquired bleeding disorder (e.g. Acquired Storage Pool Deficiency, Paraproteinemia with Platelet Inhibition)
- **4.2.8** Known inherited or acquired prothrombotic disorders, including antiphospholipid syndrome. Those with lupus anticoagulant or positive antiphospholipid serology without thrombosis are not excluded
- **4.2.9** Subjects receiving anticoagulant therapy or anti-platelet therapy (except when receiving prophylactic anticoagulant or low dose aspirin therapy for prophylaxis only with a plan to discontinue when the platelet count falls below 50,000)
- **4.2.10** Subjects with DIC (per diagnosis of patient's provider)
- **4.2.11** Subjects with WHO Grade 2 bleeding or greater within 48 hours prior to activation
- **4.2.12** Subjects requiring a platelet transfusion threshold > 10,000/μl at time of randomization
- **4.2.13** Subjects with anuria (defined as urine output < 10 mls/hr over 24 hours)
- **4.2.14** Subjects on dialysis
- **4.2.15** Subjects with creatinine ≥ 5.7 mg/dL
- **4.2.16** Subjects who are pregnant or nursing or unwilling to use contraception during and for 30 days after taking the study drug (both males and females)
- **4.2.17** Concurrent enrollment in other trials involving platelet transfusions, anti fibrinolytics, platelet growth factors or other pro-coagulant agents
- **4.2.18** Known allergy to tranexamic acid
- **4.2.19** Having been previously randomized in to the A-TREAT study at any stage of their treatment
- **4.2.20** Subjects who are unwilling to accept blood or blood component transfusions

5. TRIAL ENROLLMENT

5.1 Screening/Recruitment

- **5.1.1** Potentially eligible subjects will be identified by the subject's physician and/or by other IRB approved methods at each trial site. Research staff will commence screening to determine if the subject is eligible for enrollment based upon their medical history and laboratory results. The eligibility checklist will be completed. Each site will maintain a local log for all screened patients which will contain the case ID (assigned by DCC), site linking ID (assigned by site), and identifiable PHI in accordance with their local IRB regulations in order to correctly identify each patient. This will be done in order to prevent duplicate screening. The site staff will enter screening information via secure web-based data entry only using the case ID and site linking ID.
- **5.1.2** After obtaining permission from the subjects physician to discuss the study with the subject a trained research staff member will contact the prospective subject to describe the study and obtain consent.
- **5.1.3** After signing the consent form the subject will be entered into the study.

5.2 Stratification and Randomization

5.2.1 The subjects will be stratified according to clinical site and disease group (allogeneic transplant, autologous transplant, or leukemia) and will be balanced within varying blocks of undisclosed sizes.

5.2.2 When the consented patient's platelet count falls to < 50,000/μl with an expectation that the platelet count will be ≤10,000 for 5 days, the PI or a research staff member will access the on-line randomization system and a unique trial number will be assigned.

5.2.3 A member of the study team will contact the local investigational pharmacy to inform them of the patient's participation in the trial and study ID number.

5.2.4 When a randomized subject has a platelet count < 30,000/μl with an expectation that the platelet count would be ≤10,000/μl for 5 days, the administration of study drug will be activated, providing the date of activation is within 30 days of randomization. The date/time of activation will be time zero for the study endpoints.

5.2.5 Target enrollment will be 330 activated subjects- utilizing a 1:1 randomization schema both arms will have a target enrollment of 165 activated subjects.

5.3 Enrollment Period

Trial enrollment will take place over a period of 4 years. The expected enrollment is estimated to be 90 randomized subjects per year, with 82 activated subjects per year, across all sites.

6. INTERVENTIONS

6.1 Study Drug (Tranexamic Acid or placebo)

6.1.1 Tranexamic acid is a competitive inhibitor of plasminogen activation and, at much higher concentrations, acts as a noncompetitive inhibitor of plasmin and fibrinolysis. Patients randomized to receive TXA will take 1.3g PO (by mouth) three times a day until they meet the criteria for stopping study drug as provided in section 6.3.

6.1.1a Any patients unable to take the drug orally will receive 1.0g TXA IV (intravenous) three times a day.

6.1.1b Criteria for dose reduction in the presence of renal insufficiency are given for both PO and IV administration in section 6.5

6.1.1c Criteria for temporary discontinuation of the study drug are given in section 6.4.

6.1.2 Patients randomized to the control arm will receive matching placebo (tablets or IV solution as described in section 7.1)

6.1.3 *Rationale for dose:* The experimental doses have been chosen to be in line with the current approved indications of TXA and to be in the midrange of the doses that have been previously studied in patient populations similar to those to be accrued to this study.

6.1.4 The current indications for oral TXA (LYSTEDA) are for heavy menstrual bleeding at a dose of 1.3g t.i.d (three times daily) (total 3.9g/day) for a maximum of 5 days, with reduced dosage in patients with renal impairment. The current indication for intravenous TXA (CYKLOKAPRON) is in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. Dosage is 0.01g/kg body weight three to four times per day for 2 – 8 days after tooth extraction. Dosage is to be modified in patients with renal impairment.

6.1.5 Appendix 1 contains a listing of prior studies of anti-fibrinolytics TXA (Tables 1 and 2) and EACA (Tables 3 and 4) in patients similar to the populations to be enrolled in this study. Table 5 of Appendix 1 contains a listing of prior studies that compared TXA to EACA in any indication.

6.2 Transfusion Practice on both arms

6.2.1 Prophylactic platelet transfusions will be given when the morning platelet count is ≤ 10,000/μl

6.2.2 Therapeutic platelet transfusions may be given for active bleeding, prior to a planned invasive procedure or because of trauma, per local standard of care.

6.2.3 In instances where platelet transfusions are given for invasive procedures or trauma, the subject will return to the study platelet transfusion threshold of ≤ 10,000/μl

6.2.4 Type and dose of platelet transfusion will not be specified.

6.2.5 Clinicians can exercise discretion to transfuse platelets for any reason should they feel there is a clinical reason to do so (e.g. patient's platelet count appears to be falling just prior to a weekend).

6.2.6 If a patient develops platelet transfusion refractoriness (defined as two sequential transfusions with a 24 hour platelet increment < 5,000/μl), local practices for transfusion management will be followed. Data on use of matched platelets and alloantibody testing will be recorded.

6.2.7 The rationale for platelet transfusion over 10,000/μl will be recorded on the daily transfusion data form.

6.2.8 Patients will receive a transfusion of red blood cells per standard of care at their clinical site.

6.3 Stopping of Study Drug

Study drug will be ***permanently discontinued*** as soon as any one of the following situations occurs:

6.3.1 It has been 30 days since the subject was first activated to the randomized study drug.

6.3.2 The subject has a spontaneous increase in platelet count across 2 successive platelet measurements made at least 22 hours apart from <30,000/μl to >50,000/μl, with no intervening platelet or granulocyte transfusion, or stem cell transplant.

6.3.3 If platelet counts are ≥30,000 on 2 measurements made at least 46 hours apart with no intervening platelet counts <30,000, with no greater than a 25% decrease in platelet counts from the first such measurement to a follow-on measurement during that 46 hour period, and with no intervening platelet or granulocyte transfusion, or stem cell transplant.

6.3.4 The subject receives open label TXA, or other antifibrinolytic agent or procoagulant drug, (e.g., EACA, DDAVP, recombinant Factor VIIa, or Prothrombin Complex Concentrates). Use of these agents will be recorded in study data.

6.3.5 The subject begins anticoagulant or antiplatelet therapy.

6.3.6 The subject has visible hematuria.

6.3.7 The subject has a diagnosis of thrombosis.

6.3.8 The subject develops sinusoidal obstructive syndrome (SOS), also called Veno occlusive Disease (VOD).

6.3.9 A recurrent incident of central line occlusion. Central line occlusion is defined as inability to access or infuse through a central line requiring instillation of a fibrinolytic agent such as urokinase for clearing. It will not require radiographic or ultrasonographic evidence for diagnosis. It does not include lines that require specific patient positioning that suggests a "kink" in the line. A recurrent incident is when the definition is met on 2 separate occasions while receiving study drug.

6.3.10 The subject becomes pregnant.

If the study drug is stopped for any of the above reasons, it should not be restarted even if the platelet count later falls below 30,000.

6.4 Temporary Discontinuation of Study Drug

Study drug will be temporarily discontinued and may be restarted after resolution for the following situations:

6.4.1 A diagnosis of DIC is made by the clinical team.

6.4.2 Central line occlusion occurs (drug must be permanently discontinued if central line occlusion recurs).

6.5 Dose Adjustment for Renal Insufficiency

Study drug dosing frequency will be adjusted for renal insufficiency according to the following algorithm (dose adjustments will be based upon the first creatinine measurement on any given day):

Serum Creatinine (mg/dL)	Dosing Frequency
1.36 to 2.82	Once every 12 hours
2.83 to 5.66	Once every 24 hours
>5.66	Once every 48 hours

Patients who must begin dialysis after beginning study drug will continue to receive study drug once every 48 hours.

6.6 Other Treatment Considerations

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

7. STUDY DRUG INFORMATION

7.1 Masking of Study Drug (Tranexamic Acid or placebo)

7.1.1 Inpatient Subjects

- The investigational pharmacy at each trial site will receive randomization and distribute TXA or placebo (both IV and PO). The manufacturer of the oral drug commercially known as LYSTEDA® is Apotex Corporation and the NDC# is 60505-3638-01. The manufacturer of the IV drug commercially known as CYKLOKAPRON® is Pfizer Corporation and the NDC# is NDC 0013-1114-10. IV diluent and IV placebo may be 0.9% sodium chloride or D5W.
- A central drug distribution center, CoreRx, will prepare and package oral tranexamic acid and placebo, and then distribute blinded containers to the investigational pharmacy at each participating trial site. Containers will be coded for TXA arm vs placebo arm.
- For patients who cannot tolerate or absorb oral medication (per the discretion of the treating investigator or physician), the investigational pharmacy at each trial site will distribute TXA or placebo as equal volumes of TXA in solution or solution alone. The manufacturers, batch numbers, and sources will be reported for all doses. Sites will use the commercially available product used by their 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.

7.1.2 Outpatient Subjects

- CoreRx will prepare, package and distribute blinded containers of oral study drug to the investigational pharmacy at each participating trial site. Vials will be coded for TXA arm vs placebo arm.

7.1.3 Blinding of patients, caregivers, and study personnel

- Double blind randomization: Neither patients nor care providers nor study coordinators nor study investigators will be told which arm the patient is on.
- Among study personnel, only the unblinded pharmacists and unblinded statistician will have access to treatment assignment.
- Placebo is manufactured to be grossly similar to TXA in appearance (size, shape, color).

- To mitigate the possibility of bias in assessing treatment outcomes, research coordinators who collect outcomes data will have no contact with study drug. Details about the measures instituted to preserve assessor blind will be described in the Manual of Operations.

7.2 Administration of Study Drug

7.2.1 Study drug will be started per randomization assignment within 24 hours of the first recorded platelet count < 30,000/μl.

7.2.2 Dose Schedule

- Intravenous Administration: tranexamic acid 1 g (diluted to 50 mL) every 8 hours or placebo (50 mL) every 8 hours; both TXA and placebo will be infused over 15 to 30 minutes, then the line is flushed with 25ml saline or according to institutional standard practice.
- Oral Administration: tranexamic acid 1.3 g every 8 hours or an identical, inert placebo capsule

7.2.3 TXA for Intravenous Administration

- Tranexamic acid may be mixed with most solutions (e.g. electrolyte solutions, carbohydrate solutions, amino acid solutions and Dextran solutions).
- Tranexamic acid should not be mixed with blood products.
- The mixture should be prepared the same day the solution is to be used.
- Each mL of the sterile solution for intravenous injection contains 100 mg tranexamic acid and water for Injection to 1 mL.
- Intravenous TXA will be diluted to a 50 mL solution that will be infused over 15 to 30 minutes, and then the line is flushed with 25ml saline or according to institutional standard practice.

7.2.4 TXA for Oral Administration

- Each tablet of TXA (non-placebo) contains 650 mg tranexamic acid and the following inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, pregelatinized corn starch, povidone, hypromellose, stearic acid, and magnesium stearate.

7.2.5 Placebo for Oral Administration

- CoreRx will manufacture the placebo to be similar in size, shape, and color to the TXA tablet.
- The placebo tablets will be 650 mg microcrystalline cellulose (MCC) since there would be a risk of developing lactose intolerance in this population with the commonly used lactose filler. This avoids adding additional ingredients over the TXA. In addition to MCC, the placebo will contain magnesium stearate (0.5% or ~5mg/tablet) which is added as a lubricant for the manufacturing process.

8. STUDY VISIT PROCEDURES AND SCHEDULE

The following data will be collected as specified.

If two or more of the following study time-points fall on the same calendar date, all data required at each time-point must be collected. However, corresponding measurements that occur on both time-points do not need to be repeated. For example, if a subject receives study drug (D1 of treatment) on the same day as enrollment & randomization- all measurements to be collected on Day of Enrollment and Day of Randomization and D1 of Active Treatment must be done that day, but only one platelet count (or hemoglobin level, hematocrit level, etc.) is required.

8.1 Day of Enrollment

- Thrombotic Assessment
- Demographics and Medical History

- Weight
- Height
- Date of Birth
- Gender
- Ethnicity
- Race
- Primary Diagnosis
  - Disease
  - Current Treatment
    - Chemotherapy?
    - Transplant? If yes, date and type.
  - If receiving allogeneic transplant:
    - Donor ABO Type
    - Related Donor?
- Subject ABO Type

- Laboratory Assessments
  - Hematocrit
  - Hemoglobin
  - Platelet Count
  - WBC
  - Neutrophil (if available)
  - Serum Creatinine
  - Pregnancy Test (if not done within prior 7 days)
    - Only Females of Childbearing Potential (FCBP)
    - Urine or Serum (qualitative or quantitative) pregnancy test acceptable
  - Results of HLA antibody testing done as routine care will be recorded

- Adverse Event Assessment and Reporting- adverse events are monitored from time of consent to 30 days post discontinuation of study drug.

8.2 Days Between Enrollment and Randomization

- Thrombotic Assessment (via chart review)- *to be performed once a week*
- Laboratory Assessments

  INPATIENT SUBJECTS: to be performed daily

  OUTPATIENT SUBJECTS: to be performed twice a week
  - Hematocrit
  - Hemoglobin
  - Platelet Count
  - WBC
  - Neutrophil (if available)

- Adverse Event Assessment and Reporting

8.3 Day of Randomization

- Hemostatic/Bleeding Assessment
  - If WHO Grade 2 bleeding or greater at randomization or within prior 48 hours, do not randomize. They are eligible for randomization if bleeding resolves later.

- Thrombotic Assessment (via chart review)
- Laboratory Assessments
    - Hematocrit
    - Hemoglobin
    - Platelet Count
    - WBC
    - Neutrophil (if available)
    - Coagulation Profile (PT/INR, aPTT, Fibrinogen, D-dimer):must be drawn no longer than 24 hours before randomization or 24 hours after randomization and reviewed prior to activation
    - Serum Creatinine
    - Urinalysis
    - Pregnancy Test if > 7 days since last pregnancy test
        - Only Females of Childbearing Potential (FCBP)
        - Urine or Serum (qualitative or quantitative) pregnancy test acceptable
- Data on Platelet and Granulocyte Transfusions
    - Source of Platelets (apheresis or whole blood derived)
    - HLA or cross-match compatible
    - Reason for Transfusion
        - Met Threshold
        - Invasive Procedure
        - Active Bleeding
        - Risk of Significant Bleeding
        - Other- specify
- Data on RBC Transfusions
    - Number of Units Transfused
    - Reason for Transfusion
        - Met Threshold
        - Invasive Procedure
        - Active Bleeding
        - Risk of Significant Bleeding
        - Other- specify
- Adverse Event Assessment and Reporting

8.4 Days Between Randomization and Activation

- Hemostatic/Bleeding Assessment
- Thrombotic Assessment (via chart review) weekly
- Laboratory Assessments:

  INPATIENT SUBJECTS: to be performed daily

  OUTPATIENT SUBJECTS: to be performed twice a week
    - Hematocrit
    - Hemoglobin
    - Platelet Count
    - Serum Creatinine
    - WBC
    - Neutrophil (if available)
- Data on Platelet and Granulocyte Transfusions
    - Source of Platelets (apheresis or whole blood derived)

- HLA or cross-match compatible
- Reason for Transfusion
  - Met Threshold
  - Invasive Procedure
  - Active Bleeding
  - Risk of Significant Bleeding
  - Other- specify

- Data on RBC Transfusions
  - Number of Units Transfused
  - Reason for Transfusion
    - Met Threshold
    - Invasive Procedure
    - Active Bleeding
    - Risk of Significant Bleeding
    - Other- specify
- *OUTPATIENT SUBJECTS ONLY*: Subject Self-Assessment Bleeding Diary- provide patients with instruction on how to complete diary. This diary will be reviewed with research staff (in person or by phone) at least once a week.
- Adverse Event Assessment and Reporting

8.5 Activation

- **Days Between Activation and First Dose of Study Drug**
  - Hemostatic/Bleeding Assessment – daily while inpatient
    - If WHO Grade 2 bleeding or greater within prior 48 hours, do NOT activate-not eligible.
  - Thrombotic Assessment (via chart review) weekly
  - Laboratory Assessments:
    - Hematocrit
    - Hemoglobin
    - Platelet Count
    - Serum Creatinine
    - WBC
    - Neutrophil (if available)
    - Bilirubin (if not done within 7 days prior)
      - Check to see if bilirubin is ordered weekly while on study drug-all subjects and order if not otherwise clinically indicated
  - Data on Platelet and Granulocyte Transfusions
    - Source of Platelets (apheresis or whole blood derived)
    - HLA or cross-match compatible
    - Reason for Transfusion
      - Met Threshold
      - Invasive Procedure
      - Active Bleeding
      - Risk of Significant Bleeding
      - Other- specify
  - Data on RBC Transfusions
    - Number of Units Transfused
    - Reason for Transfusion

        - Met Threshold
        - Invasive Procedure
        - Active Bleeding
        - Risk of Significant Bleeding
        - Other- specify
    - Study Drug Administration
    - *OUTPATIENT SUBJECTS ONLY*: Subject Self-Assessment Bleeding Diary- provide patients with instruction on how to complete diary. This diary will be reviewed with research staff (in person or by phone) at least once a week.
    - Adverse Event Assessment and Reporting
- **Day 1 of Study Drug**
    - Hemostatic/Bleeding Assessment
    - Thrombotic Assessment (via chart review)
    - Ocular Assessment
      Day of first dose up to no more than 72 hours before
    - Laboratory Assessments:
      Day 1 labs ***MUST*** be drawn ***BEFORE*** the first dose of study drug is administered
        - Hematocrit
        - Hemoglobin
        - Platelet Count
        - Serum Creatinine
        - WBC
        - Neutrophil (if available)
    - Data on Platelet and Granulocyte Transfusions
        - Source of Platelets (apheresis or whole blood derived)
        - HLA or cross-match compatible
        - Reason for Transfusion
        - Met Threshold
        - Invasive Procedure
        - Active Bleeding
        - Risk of Significant Bleeding
        - Other- specify
    - Data on RBC Transfusions
        - Number of Units Transfused
        - Reason for Transfusion
            - Met Threshold
            - Invasive Procedure
            - Active Bleeding
            - Risk of Significant Bleeding
            - Other- specify
    - Study Drug Administration
    - *OUTPATIENT SUBJECTS ONLY*: Subject Self-Assessment Bleeding Diary- provide patients with instruction on how to complete diary. This diary will be reviewed with research staff (in person or by phone) at least once a week.
    - Adverse Event Assessment and Reporting

- **Day 2 of Study Drug**
    - Hemostatic/Bleeding Assessment
    - Thrombotic Assessment (via chart review)
    - Laboratory Assessments
      INPATIENT SUBJECTS: to be performed daily
      OUTPATIENT SUBJECTS: to be performed twice a week
        - Hematocrit
        - Hemoglobin
        - Platelet Count
        - WBC
        - Neutrophil (if available)
        - Serum Creatinine
    - Data on Platelet and Granulocyte Transfusions
        - Source of Platelets (apheresis or whole blood derived)
        - HLA or cross-match compatible
        - Reason for Transfusion
            - Met Threshold
            - Invasive Procedure
            - Active Bleeding
            - Risk of Significant Bleeding
            - Other- specify
    - Data on RBC Transfusions
        - Number of Units Transfused
        - Reason for Transfusion
            - Met Threshold
            - Invasive Procedure
            - Active Bleeding
            - Risk of Significant Bleeding
            - Other- specify
    - Study Drug Administration
    - *OUTPATIENT SUBJECTS ONLY*: Subject Self-Assessment Bleeding Diary- ensure patients are filling out diary correctly (in person or by phone).
    - Adverse Event Assessment and Reporting

- **Day 3 – 30 of Study Drug or up to day 30 post activation**
    - **Inpatient Subjects**
        - The following are to be performed daily:
            - Hemostatic/Bleeding Assessment
            - Thrombotic Assessment (via chart review)
            - Laboratory Assessments
                - ❖ Hematocrit
                - ❖ Hemoglobin
                - ❖ Platelet Count
                - ❖ WBC
                - ❖ Neutrophil (if available)
                - ❖ Serum Creatinine

- ❖ Check to see if bilirubin is ordered weekly while on study drug-all subjects and order if not otherwise clinically indicated
- Data on Platelet and Granulocyte Transfusions
  - ❖ Source of Platelets (apheresis or whole blood derived)
  - ❖ HLA or cross-match compatible
  - ❖ Reason for Transfusion
    1. Met Threshold
    2. Invasive Procedure
    3. Active Bleeding
    4. Risk of Significant Bleeding
    5. Other- specify
- Data on RBC Transfusions
  - ❖ Met Threshold
  - ❖ Invasive Procedure
  - ❖ Active Bleeding
  - ❖ Risk of Significant Bleeding
  - ❖ Other- specify
- Study Drug Administration
- Adverse Event Assessment and Reporting

▪ The following are to be performed weekly:

- Ocular Assessment-additionally if symptoms reported

- **Outpatient Subjects**

▪ The following are to be performed daily:

- Study Drug Administration
- Self-bleeding assessment and recorded in diary

▪ The following are to be performed twice a week:

- Hemostatic/Bleeding Assessment
- Thrombotic Assessment (via chart review)
- Laboratory Assessments
  - ❖ Hematocrit
  - ❖ Hemoglobin
  - ❖ Platelet Count
  - ❖ WBC
  - ❖ Neutrophil (if available)
  - ❖ Serum Creatinine
  - ❖ Check to see if bilirubin is ordered weekly while on study drug-all subjects and order if not otherwise clinically indicated

- Data on Platelet and Granulocyte Transfusions
  - ❖ Source of Platelets (apheresis or whole blood derived)
  - ❖ HLA or cross-match compatible
  - ❖ Reason for Transfusion
    1. Met Threshold
    2. Invasive Procedure
    3. Active Bleeding

4. Risk of Significant Bleeding
5. Other- specify

- Data on RBC Transfusions
  - ❖ Number of Units Transfused
  - ❖ Reason for Transfusion
    1. Met Threshold
    2. Invasive Procedure
    3. Active Bleeding
    4. Risk of Significant Bleeding
    5. Other- specify
- The following are to be performed once a week:
  - Ocular Assessments-additionally if symptoms reported
  - Subject Self-Assessment Bleeding Diary review with research staff (in person or by phone)

- **At Onset of ≥ Grade 2 Bleeding:** to be performed on day of onset of symptoms or at visit directly following onset of symptoms.
  - Laboratory Assessments
    - Hematocrit
    - Platelet Count
    - Hemoglobin
    - WBC
    - Neutrophil (if available)
    - Coagulation Profile (PT, aPTT, INR, Fibrinogen, D-dimer) (if available)
    - Serum Creatinine

8.6 End of Treatment: the day the subject receives their last dose of study drug OR at the next visit following last dose of study drug.

- Hemostatic/Bleeding Assessment
- Thrombotic Assessment (via chart review)
- Laboratory Assessments
  - Hematocrit
  - Hemoglobin
  - Platelet Count
  - WBC
  - Neutrophil (if available)
  - Serum Creatinine
- *OUTPATIENT SUBJECTS ONLY*: Subject Self-Assessment Bleeding Diary- to be reviewed with research staff (in person or by phone) at end of treatment.
- Adverse Event Assessment and Reporting

8.7 End of Treatment to Day 14 post Discontinuation of Study Drug (Safety Phase)

- **Inpatient Subjects**
  - Hemostatic/Bleeding Assessment and Thrombotic Assessment (via chart review) will occur daily
  - Adverse Event Assessment and Reporting
  - Weekly ocular assessments-additionally if symptoms reported
- **Outpatient Subjects**

- Outpatient subjects will complete the daily Follow-Up Subject Self-Assessment Bleeding Diary (and any necessary Self-Assessment Bleeding Forms) which will be reviewed with the research staff (in person or by phone) at least weekly
- Adverse Event Assessment and Reporting
- Weekly ocular assessments-additionally if symptoms reported

8.8 Follow Up

- **+30 Days (-1 + 6 days) post Discontinuation of Study Drug (Safety Phase)**
  - Patient will be contacted in person or by telephone (see telephone script-Appendix 3)
  - *OUTPATIENT SUBJECTS ONLY*: a final review (in person or by phone) of the Follow-Up Self-Assessment Bleeding Diary (and any necessary Self-Assessment Bleeding Forms) will be conducted and diaries and forms will be returned to the study team
  - Thrombotic Assessment (via chart review)
  - Adverse Event Assessment and Reporting
- **+120 Days (+ 3 days) post Activation of Study Drug**
  - Patient will be contacted in person or by telephone (see telephone script-Appendix 3)
  - Thrombotic Assessment (via chart review)

Table 2: Study Assessments Calendar

Study Phase		Pre-Randomization		Post Randomization / Pre Activation Phase		Activation Phase (follow for 30 days after plt <30K)					Safety Phase (30 days post drug discontinuation)			End of Study
							Active Treatment with Study Drug							
Study Assessments	Day of Enrollment	Days Between Enrollment & Randomization	At Onset of ≥ Grade 2 bleeding[3]	Day of Randomization	Days Between Randomization and activation (plt <30 K)	Days between activation and 1st dose (if applicable)	D1[1]	D2	D3-30	EOT[4]	Remainder of Activation phase (if drug stopped early)	EOT to D14 post discontinuation of study drug	30 days (+3 days) post discontinuation of study drug[11]	120 days (+3 days) post activation of study drug[11]
Demographics and Medical History	X													
Hemostatic/Bleeding Assessment				X	X[2]	X[2]	X	X[2]	X[2]	X	X[2]	X[10]		
Thrombotic Assessment[5]	X	X- weekly		X	X- weekly	X- weekly	X	X[2]	X[2]	X	X[2]	X[10]	X[8]	X[8]
Pregnancy Test[6]	X			X										
Urinalysis				X										
Hematocrit[13]	X	X[2]	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
Hemoglobin	X	X[2]	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
Platelet Count	X	X[2]	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
Serum Creatinine	X	if available	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
White Blood Cell Count	X	X[2]	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
Neutrophil Count (if available)	X	X[2]	X	X	X[2]	X[2]	X[1]	X[2]	X[2]	X	X[2]			
Coagulation Profile[7]			if available	X										
Bilirubin[14]						X			weekly					
Ocular Assessment[12]							X		X-weekly		X- weekly	X-weekly		
Study Drug (PO or IV) Administration							X	X	X					
Data on Platelet, Granulocyte, and RBC Transfusions				X	X[2]	X[2]	X	X	X[2]		X[2]			
Data on SCT	X													
Subject Self-Assessment Bleeding Diary Review[9]			X	X	X	X	X	X	X	X	X	X[10]		
Adverse Event Assessment/Reporting		Monitoring from time of consent to 30 days post discontinuation of study drug												

1- On day 1 of study treatment required laboratory tests must be drawn BEFORE the first dose of study drug is administered.
2- To be performed daily while subject is inpatient and twice a week while subject is outpatient- if done more frequently per SOC, all results will be recorded.
3- These tests to be performed at day of onset of ≥ grade 2 bleeding OR at next visit following onset of ≥ grade 2 bleeding.
4- End of Treatment (EOT) is the day when subject receives their last dose of study drug OR at next visit following last dose of study drug.
5- Thrombotic Assessments to be done via medical chart review.
6- Pregnancy test only for females of child-bearing potential (FCBP)- urine or serum (qualitative or quantitative) pregnancy test acceptable (if not done within 7 days prior)
7- Coagulation Profile is comprised of PT/INR, aPTT, Fibrinogen, D-dimer.
8- Follow-Up Thrombotic Assessments and Adverse Event Assessment/Reporting will occur via medical record review *AND* in-person or telephone contact with the subject.
9- Outpatient subjects will be expected to maintain a daily, self-assessed bleeding diary which will be reviewed with research staff (in person or by phone) at least once a week.
10- From EOT to D14 post discontinuation of study drug, *inpatient subjects* will be followed via chart review for hemostatic/bleeding assessments and thrombotic assessments. *Outpatient subjects* will complete the daily Follow-Up Self-Assessment Bleeding Diary which will be reviewed (in person or by phone) with study staff at least once a week between EOT and D14 post discontinuation of study drug. A final diary review (in person or by phone) will occur once between D14 and D21 post discontinuation of study drug and the diary (and any applicable Self-Assessment Bleeding Forms) will be returned to study staff.
11- Patient will be contacted in person or by telephone once between 14 and 21 days post discontinuation of study drug and at day 30 post discontinuation and day 120 post activation of study drug. If a member of the research staff is unable to contact the subject directly then their local physician will be contacted.
12- Per section 11, A-TREAT ocular assessments will monitor subjects' standard vision (Snellen Eye Chart), central visual field (Amsler Grid) and color perception (Ishihara test). Assessments will be done on day 1 of study drug (no more than 72 hours before randomization up to and including the day of active treatment) and will continue weekly until D14 post discontinuation of study drug.
13- Patients will receive a transfusion of red blood cells per standard of care at their clinical site.
14- Bilirubin will be collected on day 1 of activation if not completed within prior 7 days and weekly while on study drug

9. ADVERSE EVENT REPORTING

Whenever possible, investigators should report adverse events as disease or syndromes instead of reporting individual component 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, dated June 14, 2010. The criteria can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

The CTCAE includes a grading (severity) scale for 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: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3: Severe or 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 to be applied to adverse events recorded in this trial are given in Table 3 below.

Table 3: Adverse Event Definitions

Term	Definition
Adverse Event (AE)	Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.
Serious Adverse Event (SAE)	Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: • results in death[1] • is life-threatening[2] • requires hospitalization or prolongation of existing hospitalization[3] • results in persistent or significant disability or incapacity results in a congenital anomaly/birth defect • any other adverse 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
Unexpected Adverse Event	Any adverse event occurring in one or more subjects in: • a research protocol, the nature, severity, or frequency of which is not consistent with either the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product information

	and package inserts; or • the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.
Suspected Unexpected Serious Adverse Reaction	Any unexpected adverse event that: • results in death[1] • is life-threatening[2] • requires hospitalization or prolongation of existing hospitalization[3] • results in persistent or significant disability or incapacity
Unanticipated problem involving risks to subjects or others (UP)	Any incident, experience, or outcome that meets all of the following criteria: • unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; • related or possibly related to a subject's participation in the research; and • suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

***1**: Death due to the underlying disease or associated conditions will not be reported as a SAE.*
***2**: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
***3**: Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Hospitalizations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.*

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

9.1 Expected Adverse Events

9.1.1 Adverse Effects Associated with Tranexamic Acid (TXA)

- TXA is generally well tolerated by most patients. However, it can cause side effects. The most common adverse reactions seen in clinical trials (≥ 5%, and more frequent in LYSTEDA® subjects compared to placebo subjects) are headache, sinus and nasal symptoms, back pain, abdominal pain, musculoskeletal pain, joint pain, muscle cramps, migraine, anemia and fatigue. These and the following adverse events and other safety information are described in the Rev. 01/15 Code TX00N by AKORN Pharmaceuticals, Inc. ®
- Subjects may have none, some or all of the effects listed above and below and those adverse events may be mild, moderate or severe.
- Patients with a previous history of thromboembolic disease may be at an increased risk for venous and arterial thrombosis. Although clinical evidence with tranexamic acid documented in published literature shows no significant increase in thrombosis, possible risk of thrombotic complications cannot be ruled out. Venous and arterial thrombosis or thromboembolism, as well as cases of central retinal artery and central retinal vein obstruction, have been reported with Tranexamic acid.

- Gastrointestinal disturbances (nausea, vomiting, diarrhea) may occur, but have been shown to disappear when the dosage is reduced.
- Giddiness and hypotension have occasionally been reported. Hypotension has been observed when intravenous injection is too rapid. To avoid this response, the solution should not be administered more rapidly than 1 mL per minute.
- Hypersensitivity adverse events, including allergic skin reactions, anaphylactic shock and anaphylactoid reactions. A case of severe allergic reaction to Tranexamic acid was reported involving a subject on the fourth cycle of treatment. The subject experienced dyspnea, tightening of the throat and facial flushing that required emergency medical treatment.
- Rare ocular side effects have included disturbances of color vision and retinal venous and artery occlusion.
- Genitourinary side effects have included ureteral obstruction due to clot formation in patients with upper urinary tract bleeding.

9.1.2 Toxicities Related to Platelet Transfusions

- Viral infections may be transmitted from the transfusion of any blood product. Donor blood is routinely screened for the presence of hepatitis B and C, the AIDS virus (HIV 1 & 2), the HTLV viruses (1 & 2), West Nile virus and, on occasion, for cytomegalovirus. In spite of testing, rare infections with these, or other viruses, may still result from a transfusion.
- Bacterial infections can result from platelet transfusions. Platelets must be stored at room temperature and not in a refrigerator so overgrowth of bacteria may occur if there has been a break in the sterility of the system. This could result in a serious infection.
- Transfusion reactions such as chills, fever, drop in blood pressure, shortness of breath and, very rarely, shock can occur due to the transfusion of any blood products. On rare occasions, transfusions may be associated with a severe reaction that could result in lung injury, kidney failure or heart failure. Allergic reactions such as hives, rashes or, very rarely, a severe reaction that could result in death can also occur during transfusions.

9.2 Pregnancy and Nursing

- The effects of tranexamic acid on embryogenesis, spermatogenesis and reproduction in humans are unknown. The safety of the use of tranexamic acid in women who are pregnant or may become pregnant has not been established. Therefore, women of childbearing potential and fertile men will be advised to use adequate and effective contraception from the time of consent to 30 days after discontinuation of study drug.
- Patients who become pregnant during the study will be discontinued from study drug immediately and referred to an appropriate health care provider for monitoring. The event will be considered a Serious Adverse Event (SAE) and will be reported per protocol section 16.3.4. The patient will continue to be followed per protocol, with additional follow-up for pregnancy outcome.
- Tranexamic acid is excreted into breast milk, therefore nursing subjects are excluded from the study. If subjects are pumping breast milk, and the milk is destroyed, then they may be included.

10. HEMOSTATIC/BLEEDING ASSESSMENTS

Bleeding will be recorded by the well-established bleeding assessment tool, validated in PLADO[4] & TOPPS[6] and refined for this study. Rates of recorded bleeding are known to vary considerably between trials. Reasons for this variability have been explored and published through a study organized by the BEST collaboration, and include different patient groups and bleeding definitions and variable follow up periods[18].

In this trial, a number of measures will be taken to standardize documentation and recording of bleeding, including trained assessors, monitoring and education. In the recent TOPPS study, completeness of bleeding outcome documentation was excellent: A bleeding assessment was completed on 93% (8405/9030) of days for patients in the non-prophylactic group, and 97% (8733/8970) of days in the prophylactic group. The majority of patients in both arms had bleeding information completed on each study day (median non-prophylactic 30 days (IQR 29 to 30); median prophylactic 30 days (IQR 30 to 30)).

10.1 Inpatient Subjects

Bleeding assessments will be performed by means of a physical assessment of the patient, patient interview (if possible), and a review of the patient chart and laboratory data. Research staff will perform the physical assessment and interview of the patient ***before*** reviewing the patient's chart and laboratory data as to allow an objective assessment without the bias that might be introduced by performing the chart and laboratory reviews first. Research staff will perform the hemostatic assessment at approximately the same time each day.

10.2 Outpatient Subjects

All outpatient subjects (including those who are discharged from inpatient status prior to completion of the initial trial period [30 days from randomization]) will be trained in the completion of a daily Self-Assessment Bleeding Diary. The diary will ask the subject to respond "yes" or "no" as to whether they have experienced any bleeding for each body system on that day. Information will be provided to the subject describing how to report degree of bleeding in relation to amount of blood present, size of bruising, etc. Subjects will have their Self-Assessment Bleeding Diary reviewed by research staff *at least weekly,* either in person or over the phone. Patients who are seen in the outpatient clinic whilst still within the 30 day trial period will have a bleeding assessment completed by the local research staff in addition to the daily self-assessment. Self-assessment data will not be used as the outcome unless there is no medical assessment form.

All outpatient subjects will be contacted by the research staff between day 14 and 21 post discontinuation of study drug a diary review and to confirm arrangements to collect all relevant forms. All forms will be entered into the trial database.

11. SAFETY ASSESSMENTS

Thrombotic assessments will be performed via a review of medical chart notes and imaging studies by trained research staff at the following time points (see Table 2: Study Assessments Calendar for further information regarding timing of assessments):

11.1 Thrombotic Assessments

11.1.1 Inpatient Subjects

11.1.1a *Weekly* in the days between Day of Enrollment and Day of Randomization
11.1.1b Day of Randomization
11.1.1c *Daily* during active treatment with study drug
11.1.1d Day 30 post first dose of study drug
11.1.1e End of Treatment
11.1.1f +1 day post last dose of study drug
11.1.1g *At least Once* between 14 and 21 days post discontinuation of study drug
11.1.1h Day 30 post discontinuation of study drug
11.1.1i Day 120 post activation of study drug

11.1.2 Outpatient Subjects

11.1.2a *Weekly* in the days between Day of Enrollment and Day of Randomization
11.1.2b Day of Randomization
11.1.2c *Twice a week* during active treatment with study drug
11.1.2d Day 30 post first dose of study drug
11.1.2e End of Treatment

11.1.2f +1 day post last dose of study drug
11.1.2g *At least Once* between 14 and 21 days post discontinuation of study drug
11.1.2h Day 30 post discontinuation of study drug
11.1.2i Day 120 post activation of study drug

11.2 Ocular Assessments

11.2.1 All subjects will have ocular assessments of standard vision using the Snellen Eye Chart, central visual field using the Amsler Grid, and color perception using the Ishihara color plates no more than 72 hours before randomization up to and including the day of active treatment, then weekly until two weeks post discontinuation of study drug.

11.2.2 Subjects should be instructed to report visual and ocular symptoms promptly to study staff, and to have a vision check by study staff or physician thereafter.

11.2.3 *Rationale:* The package inserts for both oral (LYSTEDA) and IV (CYKLOKAPRON) TXA include warnings for ocular and visual changes that have been observed in both Pre-clinical animal studies and post-marketing surveillance. The package insert notes that no such changes were observed during clinical trials involving treatment for weeks to months of TXA, however it does recommend monitoring of visual acuity at regular intervals, with discontinuation of therapy if visual or ocular symptoms occur.

11.2.4 In this study, the patients will often be receiving chemotherapies and steroids that are associated with similar visual and ocular changes, though the exact incidence of such changes is not well-characterized. Through the specified monitoring of visual and ocular signs and symptoms, we address the possibility that TXA might exacerbate the effects of the chemotherapies. All visual or ocular AEs that are CTCAE Grade 3 or higher will be reported to the independent DSMB in an expedited fashion, in order that any differential incidence of such changes across treatment arms can be assessed and lead to protocol changes as appropriate.

12. LOSS TO FOLLOW UP

12.1 Death

Death will be recorded on the end of study form and will be characterized by time from consent and according to whether the investigator attributes mortality due to bleeding, due to thrombosis, or due to other causes.

12.2 Withdrawals

Subjects are free to stop study drug at any time. If this occurs, the date and time that study drug is voluntarily stopped will be recorded, along with the reason the subject so elected. In the event the subject elects to stop study drug, they will still be followed for all study outcomes according to study protocol.

Subjects are also free to withdraw their consent for further participation in the trial at any time. If this occurs, subjects will be asked to grant consent for the study team to passively monitor their clinical outcomes for major clinical events. 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.

An End of Study form will be completed, which will detail whether the subject is:

12.2.1 Stopping study drug, but continuing all other protocol specified procedures and monitoring.

12.2.2 Stopping study drug and protocol specific procedures and monitoring, but allowing passive monitoring of their medical record and follow-up for vital status 30 days after their last dose of study drug.

12.2.3 Discontinuing all further contact with study investigators.

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 and the reason for withdrawal recorded if possible for all occurrences.

13. END OF STUDY

Subjects will exit the study after the day 120 post activation of study drug time point requirements are fulfilled.

14. STATISTICAL CONSIDERATIONS

14.1 Rationale and Objectives

The hypothesis is that in patients with hematologic malignancies, during a period of severe thrombocytopenia, prophylactic use of anti-fibrinolytic therapy with TXA would decrease bleeding and the demand for platelet transfusions. Additional benefits for patients might extend to improved in-patient experience and earlier discharge home.

14.1.1 Primary Efficacy Endpoint- Assessment of the TXA effect on bleeding will primarily consider the difference in the proportion of patients on each arm having bleeding of WHO grade 2 or above at some point during the first 30 days post activation of study drug.

14.1.2 Secondary Efficacy Endpoints- Assessment of the TXA effect on demand for platelet transfusions will primarily consider the difference between the treatment arms in the average number of platelet transfusions per patient during the first 30 days post activation of study drug. A composite endpoint incorporating both bleeding and all cause mortality will consider the difference between the treatment arms in the average number of days alive without WHO grade 2 bleeding or greater during the first 30 days after activation. In order to protect against inflation of the type 1 error, a closed testing procedure will be used in which the statistical significance of any observed effects of TXA on the secondary endpoints will only be interpretable if a statistically significant effect of TXA on the primary efficacy endpoint is observed.

14.1.3 Supportive and Exploratory Efficacy Endpoints- Additional endpoints examining other measures of bleeding, transfusions, and clinical outcomes associated with TXA treatment will be used to further support any statistically significant effects observed for the primary and secondary efficacy endpoints. The statistical significance of these additional endpoints will not be directly interpretable owing to the multiple comparisons.

14.2 Randomization

Patients will be randomized to antifibrinolytic therapy with TXA or to placebo in a 1:1 fashion, stratified by site and disease group (allogeneic transplant, autologous transplant, or leukemia). Randomization will further be balanced within blocks of varying, undisclosed sizes.

14.3 Analysis Populations

Subjects will be grouped according to randomization groups: TXA versus placebo. Unless otherwise specified, all efficacy analyses will be by a modified intention to treat (mITT) strategy among activated subjects as described below. All subjects who were activated to study drug will be included in the analyses in the treatment group to which they were randomly assigned. Subjects who were activated for study drug will be included in the analyses, even if they stop study drug "early", cross over between treatment groups, or receive prophylactic transfusions not in accordance with the protocol.

14.3.1 Efficacy Population

The mITT population used for efficacy analyses will be comprised of all randomized patients for whom an order for administration of study drug is activated. Efficacy

analyses on these patients will use data gathered from the time the order for study drug was activated until 30 days post activation. Randomized patients who develop exclusion criteria prior to activation of study drug and who thus are excluded from receipt of study drug and patients whose platelet counts never drop below the 30K threshold for activation of study drug will not be included in the primary efficacy population.

Rationale: Owing to the emergent nature of treatment of thrombocytopenic patients, patients are randomized in a double blind fashion to the treatment arms when platelet levels drop below 50K. Because the treating physicians are blinded to treatment arm assignment, no bias in activation of the study drug is anticipated. By using the time that the study drug is activated as the criterion for inclusion in the mITT population, we guard against differential delays in pharmacy preparation of placebo versus study drug.

14.3.2 Safety Population

The population used for safety analyses will be all patients who receive any amount of study drug. Follow-up for mortality and thrombotic events will occur at 120 days post activation. Other adverse events and serious adverse events will be collected for 30 days post discontinuation of study drug, with visual examinations occurring weekly for two weeks after discontinuation of study drug. SOS (VOD), AEs, and SAEs will be based on clinical diagnosis and patient report during the surveillance period. The frequency of follow-up will differ between inpatients and outpatients, with the former based on daily visits by the research coordinators and the latter based on patient diaries and semiweekly clinic visits (while still on study drug) or weekly contacts (after discontinuation of study drug

14.4 Competing Risks

14.4.1 Death

Owing to the seriousness of the patients' underlying medical condition and based on PLADO data it is anticipated that fewer than 5% of patients might die from their disease or its treatment prior to full determination of the primary and/or secondary endpoints (e.g., dying within 30 days without experiencing significant bleeding). Such "competing risks" pose both scientific and statistical dilemmas. In terms of the scientific aims, the primary analysis of A-TREAT data will use an approach that presumes independence of death and future bleeding that is conditional on the hematologic and transfusion history for patients prior to death. The interpretation of the resulting comparisons is as an estimate of the effect of TXA on bleeding rates in a population in which the treatment of the underlying medical condition (e.g., infections secondary to chemotherapy) has improved to the point that patients are no longer at risk of early death. The statistical treatment of this approach is described in 14.5.

Rationale: There is of course no way to know whether patients who die early have an increased or decreased propensity to bleed in the absence of the competing risk. Ultimately, the impact of the proposed "missing-at-random" (MAR) analysis of these incomplete observations will have to be examined in a series of sensitivity analyses described in 14.5.4. Alternative strategies considered by the A-TREAT investigators included using death as a part of a composite endpoint that includes bleeding and all cause mortality. However, such an analysis does not truly protect against the possibility that a treatment might cause a minor increase in death and a more major decrease in bleeding rates. Even with a composite endpoint the overall mortality rates would thus need to be examined separately and there could even be nonsignificant trends toward increased mortality on TXA that would have to be considered carefully. Hence, the A TREAT investigators decided on an approach consistent with their clinical impression that there was not a strong dependence between death from other causes and propensity to bleeding, and to use the secondary and supporting endpoints and sensitivity analyses to explore the robustness of the analysis results to other assumptions

14.4.2 Discharge from Hospital

Patients discharged from the hospital prior to 30 days post randomization will not have as intense surveillance for study events as will those who remained in the hospital. They will have completed a daily bleeding diary and be contacted to determine any clinically important bleeding events. Absence of a bleeding event that leads to hospitalization or treatment by doctor/healthcare worker or categorized as such in the daily bleeding diary will be judged as absence of grade 2 or higher bleeding by WHO criteria. Similarly, such patients will be imputed to have not had transfusions.

14.5 Statistical Analysis Models

All statistical inference will be based on a two-sided 0.05 level of significance and two-sided 95% confidence intervals. Full details regarding statistical analysis models will be presented in a Statistical Analysis Plan completed prior to the first unblinded analysis of the data.

14.5.1 Primary Endpoint

The odds of bleeding at WHO grade 2 level or above will be analyzed in a logistic regression model adjusting for treatment arm, clinical site as a factored variable, and disease group (allogeneic transplant, autologous transplant, or leukemia) as a factored variable.. The test statistic will be based on the score statistic for the treatment arm parameter from the logistic regression model with adjustment for multiply imputed missing data.

14.5.2 Secondary Endpoints

The secondary endpoints of mean number of platelet transfusions and the mean number of days alive without WHO grade 2 level or above bleeding will each be analyzed in a linear regression model adjusting for treatment arm, clinical site as a factored variable, and disease group (allogeneic transplant, autologous transplant, or leukemia) as a factored variable. The test statistic will be based on the Wald statistic (parameter estimate divided by its standard error) as computed for the treatment arm parameter from the linear regression model using the Huber-White sandwich estimator for standard errors to account for possible heteroscedasticity and adjusting for multiply imputed data.

14.5.3 Additional Analyses

Analysis of the supportive and exploratory endpoints will be conducted using regression models adjusting for treatment arm, clinical site as a factored variable, and disease group (allogeneic transplant, autologous transplant, or leukemia) as a factored variable. Linear regression will be used for endpoints measuring the days free of bleeding and highest grade of bleeding, logistic regression will be used for binary endpoints, and proportional hazards regression will be used for times to event. The Huber-White sandwich estimator of the standard error will be used to allow for departures from the model based variance estimates, and adjustment will be made for multiply imputed missing data.

14.5.4 Missing Data

Patients will be followed for all clinical trial outcomes regardless of their adherence to the prescribed regimen for the study drug (TXA or placebo). Very few patients are expected to withdraw consent, though there will undoubtedly be some cases in which the data are missing for one or more of the primary, secondary, or supporting analyses due to withdrawal of consent or competing risks as described in 14.4.

Initial analyses of primary and secondary endpoints will be based on missing-at-random (MAR) models that condition on the patients' prior history of platelet levels, platelet and red blood cell transfusions, and days since activation of study drug. In the MAR model, data will be imputed by assuming that patients with missing data will be presumed to have distributions of outcomes the same as that observed in comparable patients who have complete data.

Sensitivity analyses will use missing not at random (MNAR) models to reflect increased or decreased odds of bleeding among patients with incomplete data. Each treatment arm will be parameterized separately, and the robustness of any estimated treatment effect to those varying levels of dependence between early death or withdrawal of consent and incidence of

bleeding will be quantified. Additional models will consider separate mechanisms for early death and withdrawal of consent.

14.6 Sample Size and Precision of Statistical Inference

14.6.1 Minimal Clinically Important Difference

Based on results observed in the PLADO study for patients who meet the general eligibility criteria for the A-TREAT study, it is anticipated that 57% of eligible patients would experience WHO Grade 2 bleeding or higher in the absence of antifibrinolytic therapy. In such a background setting of bleeding, the study investigators anticipate that less than a 10% relative reduction in bleeding rates would not be sufficient to substantially change clinical practice, because the absolute risk reduction of 5.7% would mean that it would be necessary to treat approximately 17.5 patients in order for the treatment to have impact on 1 patient ("Number Needed to Treat" (NNT) = 17.5). As much as a 25% relative reduction in bleeding rates would likely be judged sufficient to change clinical practice, because with an absolute risk reduction of 14.25%, the NNT of approximately 7 patients might be acceptable, provided no new safety issues related to antifibrinolysis in the thrombocytopenic population are uncovered. The A-TREAT investigators hypothesize that TXA will be associated with a relative reduction of 30% or higher (absolute reduction of 17%) based on observational data relative to their prior clinical experience.

14.6.2 Sequential Stopping Rules

The conduct of the A-TREAT study will be overseen by an independent Data and Safety Monitoring Board (DSMB) who will enhance patient safety by monitoring study progress and integrity, incidence of AEs and SAEs, and interim estimates of treatment effect on bleeding. The DSMB will be guided by a group sequential stopping rule to judge the scientific and statistical credibility of interim results on the bleeding endpoints.

While the exact stopping rule will be chosen in discussion with the DSMB (and documented in the Statistical Analysis Plan finalized prior to the first interim analysis at which the DSMB will see unblinded data), the A-TREAT investigators propose a stopping rule that would allow early stopping only if a one-sided level 0.20 O'Brien-Fleming stopping boundary suggested that TXA was associated with more bleeding than placebo. There would be no early stopping boundary for efficacy of TXA over placebo, with the final critical value for efficacy providing a one-sided 0.025 level of significance.

The following table presents example stopping boundaries that might correspond to an observed combined event rate of 0.485 (such as might be observed with 57% events on the placebo arm and 40% events on the TXA arm). Using the R package RCTdesign (or equivalently, S-Plus S+SeqTrial), a stopping boundary having three analyses at 50%, 75% and 100% of the planned sample size and with a level 0.2 O'Brien-Fleming boundary for harm would be computed using the RCTdesign code:

```
seqDesign(prob.model = "prop", null.hypothesis = 0.57,
    alt.hypothesis = 0.4, nbr.analyses = 3,
    sample.size = c(165, 248, 330), test.type = "two.sided",
    power = "calculate", alpha = c(0.025, 0.2),
    P = c(Inf, 1))
```

For this example stopping boundary, the following table presents the critical values for harm and the corresponding adjusted statistical inference at each of the formal interim analyses. Critical values are expressed in terms of the crude estimate of treatment effect (TXA bleeding rate minus control bleeding rate), a Z statistic, and a one-sided fixed sample P value testing for harm. The adjusted statistical inference is a point estimate based on the bias adjusted mean and 95% confidence intervals and one-sided P values testing for harm using the likelihood ratio ordering of the outcome space.

Analysis		Stopping Boundaries			Adjusted Inference		
	N	Crude Estimate	Z	Fixed P val	Estimate	95% CI	One-sided P value
50%	165	0.111	1.440	.075	0.095	(-.004, .181)	0.123
75%	248	0.074	1.175	.120	0.059	(-.018, .132)	0.178
100%	330	0.055	1.019	.154	0.043	(-.022, .115)	0.200

Rationale: Owing to the need for adequate safety data, even if TXA is associated with markedly less bleeding than placebo, there is an imperative to gather safety data on the full sample size. Because TXA is currently being used off-label in the thrombocytopenic setting, it is important to document any harm due to TXA treatment, rather than just documenting the absence of a markedly beneficial effect.

14.6.3 Sample Size

Calculation of sample size and statistical power were made using S+SeqTrial based on the chi-squared test of association, which is equivalent to the score test from simple logistic regression. Based on 1:1 randomization, a one-sided level of significance 0.025, a design alternative hypothesis of 30% relative reduction in bleeding rates (57% on the placebo arm and 40% on TXA), a sample size of 330 subjects (165 TXA, 165 placebo) will provide 88% statistical power to declare statistical significance on the primary endpoint. This sample size will provide 74.8% statistical power to detect a 25% relative reduction in bleeding rates (57% vs 42.75%).

14.6.4 Precision of Inference for Efficacy

With the planned sample size and a placebo bleeding rate of 57%, an observed absolute decrease in WHO grade 2 or above bleeding of 10.6% (so 57% on placebo, 46.4% on TXA) would be judged statistically significant. Such an absolute difference in rates corresponds to a NNT of 9.4. If the baseline placebo bleeding rate were instead 40%, the threshold for statistical significance would be an absolute reduction of 10.14% (NNT = 9.9), and a baseline placebo rate of 70% would have a threshold of 10.35% (NNT = 9.7). These results are judged to be of the magnitude to possibly affect clinical practice, and allow for some added loss of precision with multiply imputed missing data.

14.6.5 Precision of Inference for Safety

This study is not powered to establish the definitive safety of the treatment with respect to the frequency of VTE. However, an observed difference in frequency of VTE of 3.7% on the placebo arm and 5.5% or less on the TXA therapy arm would result in a 95% confidence interval that excluded a relative risk of 3.0.

14.7 Feasibility of Recruitment

The three clinical sites have proven success recruiting patients in the PLADO study at a rate that would predict success in achieving accrual of 330 activated patients during the planned 4 year accrual period.

The following table documents how that prior success translates into the A-TREAT targeted enrollment:

	PLADO (3.5 yr)	**Annualized Rate**	**Four Year Projections**	**A-TREAT Target**
Puget Sound Blood Center at the University of Washington	107	30.6	122	110
University of Pittsburgh	119	34.0	136	110
University of North Carolina	99	28.3	113	110
Total	**326**	**92.9**	**371**	**330**

It can be seen that, based on annualized rates achieved in the PLADO study by these sites, there is 12% excess capacity.

If accrual to the study does not meet expectation additional sites will be recruited.

15. TRIAL MONITORING

15.1 Clinical Site Monitoring

Study monitoring will be the responsibility of the Data Coordinating Center (DCC). Upon successful approval of the protocol and establishment of the regulatory file, the clinical monitor will establish a clinical monitoring plan. To ensure that the investigator and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of complete records.

Monitoring visits by a sponsor's representative-designated clinical monitor will be scheduled to take place during the study at appropriate intervals and after the last subject has completed the study. A report of monitoring observations will be provided to the site PIs for corrective actions.

15.2 Direct Access to Data

Study subjects will be identified on CRFs by a unique study subject ID code and on source documents by name or study subject ID code. 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 study subject. Representatives from the DCC, IRB and the 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. Medical and research records will be de-identified before 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.

15.3 Audits and Inspections

Authorized representatives of the sponsor, IRB or FDA may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The investigator should contact the sponsor's representative and DCC and the study sponsor immediately if contacted by a regulatory agency about an inspection.

15.4 Source Data Verification

A monitoring plan between the sites and the Data Coordination Center will be written and followed. A proportion of the CRF data will be checked against source documentation, including 100% of the first three patients recruited to the study at the site and key endpoint data of all patients recruited thereafter. Particular attention will be paid to those patients who experience Serious Adverse Events and/or Serious Transfusion Reactions. All CRF data, whether or not subject to source data verification, will be checked by each site for completeness and consistency before being sent to data management. All consent forms will be monitored.

15.5 Quality Assurance and Quality Control of Data

In addition to source data verification, quality control of the clinical bleeding assessments will be on-going throughout the trial. This will include initial training of the clinical study staff, training of patients in proper self-assessment, and a program of duplicate bleeding assessments to ensure consistency in completion of the clinical bleeding assessment forms. Standard guidelines will be followed.

Good Clinical Practice Guidelines require that investigators maintain information in the subject's medical records, laboratory reports, clinical charts etc. that corroborate data recorded on the CRFs. In order to comply with these source documentation requirements, the following information should be maintained:

- Medical history/physical condition of the subject before enrollment sufficient to verify protocol entry criteria.
- Dated and signed notes for specific results of procedures and exams.

15.6 Confidentiality

Data will be held securely in locked files or an encrypted database at the DCC and at each trial site.

Patients will be identified only by study specific identification number on all data that are sent to the DCC.

No personal identifier will be used in any publication or communication used to support this research study. The study subject's ID code will be used in the event it becomes necessary to identify data specific to a single study subject.
HIPAA requires that researchers obtain the study subject's permission (HIPAA Authorization) to use and disclose health information about the subject that is either created by or used in connection with this research. The information includes the entire research record and supporting information from the study subject's medical records, results of laboratory tests, and both clinical and research observations made during the study subject's participation in the research.

In this research, the study subject's health information will be collected and used to conduct the study; to monitor the study subject's health status; and any adverse events. Health information is used to report results of research to the sponsor's representative and federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. After the study ends, each study subject has the right to see and receive a copy of his or her information.

The site PIs will be responsible for retaining sufficient information about each study subject, that is name, address, telephone number, and identity in the study, so that the sponsor's representative, and other regulatory authorities may have access to this information should the need arise.

15.7 Ethical Conduct of the Study

This study will be conducted in accordance with 21 CFR Part 50 and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the CFR. The co-PIs confirm this by signing this study protocol.

16. RECORDS AND REPORTS

16.1 Case Report Forms

The study will used a web based data entry system.

Case Report Forms (CRFs) will be used to collect all subject study data during the course of the study. The Principal Investigator at each clinical site or a predetermined designated individual shall be responsible for completion of the CRFs. All protocol deviations shall be documented and a justification for any missed assessments shall be provided on the protocol deviation log. Completion of the CRFs will be on-line via a secure password protected website. Queries will be resolved via the secure web based data entry system; those that cannot be resolved in this way will be completed via email or phone communication and corrections will be made to appropriate CRFs.

The Investigator will allow NHLBI, the FDA, or other regulatory bodies to review the study files, subject CRFs, medical records and other study-related documents.

16.2 Record Retention

The sites must maintain the signed Informed Consent Forms, CRFs, study documentation (listed above) and source documents for at least 3 years after study completion or termination. In the event of an FDA audit, the Investigator must allow FDA access to the study records for inspection and copying.

16.3 Data Management

Data will be collected by individual sites and provided to the DCC in the manner described below.

16.3.1 Data Entry

The DCC will provide secure web-based HTML forms to collect necessary information from the participating sites. Web entry forms will have dynamic features such as immediate checks on data and relationships within a form and between forms. Details and clarification about data items will be provided using pop-up windows and links to appropriate sections of the on-line version of the Manual of Operations. Data encryption and authentication methods will be used. Additional features of the web entry forms will include: form transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms.

16.3.2 Database Management

The DCC will use a two-tiered database system. A front-end database serves the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred periodically (e.g. weekly) to a data format that can be utilized by statistical software packages. These will be the basis for queries, analyses and monitoring reports. Database files will be maintained on a password protected computer in a secure location behind a firewall.

Various versions of the database are kept as needed, e.g. for quarterly performance reports. Back-ups of data and programs will be performed regularly. Access to data will be limited to those who need access to perform their tasks.

16.3.3 Trial Specific Exceptions to Expedited SAE Notification and Reporting

All deaths will be reported on the end of study data form. Although death as a result of disease progression is not an SAE it will be reported within 24 hours to the DCC, see section 16.3.4).

Due to the seriousness of the disease in this study, the following situations that would fulfil the definition of an SAE are excluded from expedited notification and may be reported to the DCC within **5** working days.

- Elective hospitalization to simplify treatment or procedures
- Elective hospitalization for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial treatment
- Admission to the intensive care unit related to the disease
- Severe Sepsis
- Disease Progression
- Any other serious event related to the underlying disease or medication used to treat the disease

16.3.4 Serious Adverse Events

All serious adverse events, including death of an actively participating subject, must be reported to the DCC within **24 hours** by e-mail. This will allow investigation into the cause of death to determine if it was a result of disease progression or potential SAE. The Serious/Unexpected Adverse Event Form must be sent to the DCC within **48 hours**. The Serious Adverse Event Form will be entered into the web based data entry system by the site and further information and follow up will be prompted by the DCC via the SAE adjudication system in place.

Serious adverse events, including death, will be monitored continuously by the DCC as data are received.

When a transfusion related adverse reaction/event or other medical event occurs, the investigator responsible for the care of the patient must first assess whether the event is serious using the definitions given in Figure 3 (section 9).

The clinical staff responsible for the care of the subject remains responsible for reporting all adverse transfusion reactions/events according to normal procedures.

Information about the following events will be collected:

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

The investigator must assess the causality of all Serious Adverse Events using the definitions in Table 4.

If the causality assessment is deemed unrelated the event is classified as a SAE.

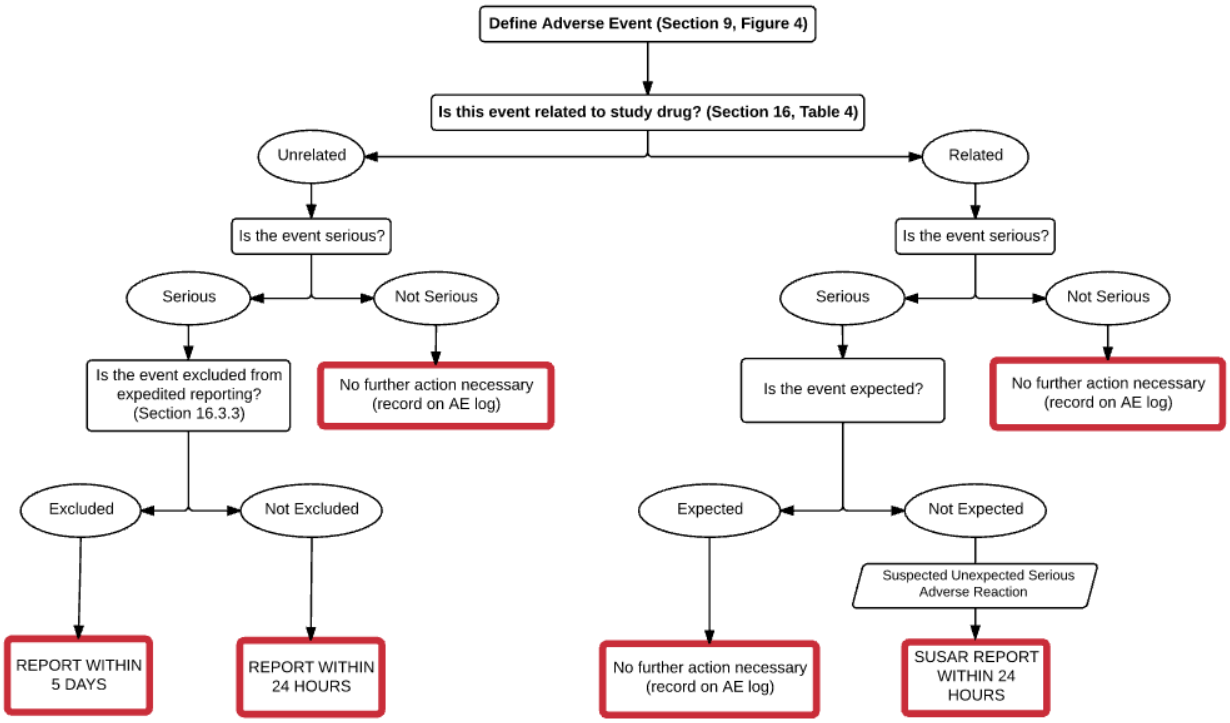
If the causality is assessed as either possibly, probably or definitely related then the event is classified as a Serious Adverse Reaction.

Table 4: Definitions of Causality/Attribution

Relationship	Description
Unrelated	There is no evidence of any causal relationship. Event clearly related to other factors (e.g., clinical state, other therapies; concomitant drugs).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	Sequence of event is compatible with study drug, device, or procedure and cannot be explained by other factors without much doubt
Definitely	Sequence of event is compatible with study drug, device, or procedure and beyond doubt cannot be explained by other factors

If the event is an SAE the Investigator must assess the expectedness of the event as well.

Figure 5: Investigator Assessment of Adverse Events



The DCC should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting (i.e. any expected or unexpected Serious Adverse Reaction or other serious event such as a major bleed [grade 3 or 4]). Investigators should notify the DCC of all such events occurring during the study period.

The SAE form must be completed by the Investigator (consultant/physician named on the signature list and delegation of responsibilities log who is responsible for the subject's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. 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, sign and then upload to the web site, or re-fax/hand deliver to the DCC as soon as possible. The initial report shall be followed by detailed, written reports as requested by the DCC.

Follow-up: 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 to the DCC 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 must not be used on any correspondence.

Site staff must notify their local IRB of any event that is classified as a suspected unexpected serious adverse reaction (as per the institutions standard local procedure).

DCC Responsibilities: The Primary Investigator or a medically qualified delegate will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both the opinions of the patient's physician and the trial site PI will be provided in any subsequent reports. All SAE reports will be reviewed by the DSMB, as directed by the DSMB and as a listing at their review of the trial every 6 months.

17. INSTITUTIONAL REVIEW BOARD (IRB)

No subject will be enrolled into the study until the IRB has approved the protocol and the informed consent form. Copies of all submissions to and correspondence (approvals and disapprovals) from the IRB must be maintained in a regulatory file at the study site.

18. TRIAL COMMITTEES

18.1 Trial Steering Committee (TSC)

A Trial Steering Committee will provide oversight of this trial, which will be conducted according to the principles of GCP. Members of the TSC include PIs from the trial sites and the PI of the DCC.

18.2 Data and Safety Monitoring Board (DSMB)

The conduct of the trial and the safety of patients accrued to the trial will be monitored by an Independent DSMB agreed upon by the NHLBI. Membership will be independent of study investigators and have no financial or intellectual conflicts of interest. The DSMB will be comprised of 4-6 members, including hematologists, a biostatistician, and an ethicist. The DSMB will be guided by a DSMB Charter that delineates the roles and responsibilities of the DSMB, including delineation of the lines of communication between study clinical investigators, study data coordinating center, and the NHLBI.

The DSMB will meet via teleconference every 6 months to review study progress (recruitment, adherence to protocol) and safety data, including serious adverse events, adverse events, bleeding events, and mortality. The DSMB may also request more frequent meetings as necessary to protect study integrity and study safety.

APPENDIX 1: TRANEXAMIC ACID AND EPSILON AMINOCAPROIC ACID STUDIES
Table 1: Tranexamic Acid Studies (Characteristics)

Study	Type of study	No. of pts	No. of pts receiving TA	No. of pts plt refractory/ allo-immunization	Diagnosis of pt	Treatment of underlying disease	Tranexamic acid dose	Tranexamic acid frequency	Tranexamic acid route	Treatment started	Treatment stopped	Platelets given
Randomized studies												
Avvisati 1989[19]	RCT	12	6	NR	APL	Chemo	2g	8hrly	IV in 500ml 5% glucose	1st day of antileukemic Rx	After 6 days	Prophylactic
Fricke 1991[20]	RCT Cross-over	8 Only 3 completed study	8	At least 3	7 AA 1 MDS	NR	20mg/kg	8hrly	Oral	After 4 day trial period to assess drug tolerance	Successive 4/52 courses or until grade 2 bleeding	Therapeutic
Shpilberg 1995[12]	RCT	56	26	NR	AML 38 induction 18 consolidation	Chemo	1g	6hrly	Oral	Platelets < 20 or rapidly falling and < 50	Platelet count > 20 for 2 consecutive counts	Therapeutic
Non-randomized studies												
Ben-Bassat 1990[21]	Not controlled	54	54	NR	Newly diagnosed AML	Chemo	1g	6hrly	Oral IV if unable to tolerate PO	Platelet count < 50	Platelet count > 20	Therapeutic
Sanz 2010[22]	Historical control	732	560	NR	Induction APL patients	Chemo	100mg/kg/day	Continuous infusion	IV	Platelets <50	Platelets > 50	Prophylactic >30

Table 2: Tranexamic Acid Studies (Results)

Study	Type of study	No. of pts	Diagnosis of patient	Thrombotic risk	Bleeding	Death due to bleeding	Platelet transfusions	Platelets given
Randomized studies								
Avvisati 1989[26]	RCT	12	APL	No thromboembolic events observed	Cumulative hemorrhagic scores TA 3 C 42 (P = 0.0045)	Not reported	Extra platelet Tx TA = 69 Tx C = 222 Tx P = 0.045	Prophylactic
Fricke 1991[38]†	RCT Cross-over	8 Only 3 completed study	7 AA 1 MDS	Not reported	No evidence for difference in bleeding from mouth (p >0.2) or nose (p = 0.07). TXA more bleeding for skin (P<0.02)*	1 patient died from ICH 4 days after starting Rx	Failure for each section of the study was need for plt Tx TA 8/26 failed C = 9/23 failed	Therapeutic
Shpilberg 1995[27]	RCT	56	AML 38 induction 18 consolidation	No thromboembolic events observed	Induction TA 6.2±2.9 C 4.5±3.6 Consolidation TA 1.1±1.4 C 2.6±2.2 (P <0.5)	None	Induction (units) TA 22.1±13.2 C 23.1±11.7 Consolidation (units) TA 3.7±4.1 C 9.3±3.3 (P <0.5)	Therapeutic
Non-randomized studies								
Ben-Bassat 1990[39]	Not controlled	54	Newly diagnosed AML	No thromboembolic events observed	Major bleeding 6/78 induction courses Major bleeding 0/53 consolidation courses	1 death due to bleeding	Induction 4.6 ± 4.1 Consolidation 1.7 ± 1.8 transfusions	Therapeutic
Sanz 2010[40]	Historical control	732	Induction APL patients	Tranexamic acid use RR 1.96 (P = 0.049)	Not reported	No difference 5.1% (9 of 175). 5% (28 of 561)	Not reported	Prophylactic >30

†This study had major methodological limitations and any results should be treated very cautiously.

* It could not be determined whether the higher incidence of bleeding in the TXA arm was due to the higher number of days patients were on the study prior to failure as this was not reported.

Table 3: Epsilon Aminocaproic Acid Studies (Characteristics)

Study	Type of study	No. of pts	No. who rec'd EACA	No. plt refractory/ allo-immunization	Diagnosis of patient	Treatment of underlying disease	EACA dose	EACA frequency	EACA route	Treatment started	Treatment stopped	Platelets given
Randomized studies												
Gallardo 1983[23]	RCT	19	9	NR	15 AML 4 ALL (1 patient inevaluable)	Chemo	Loading dose 100mg/kg 12-24g/day thereafter	NR	NR	Platelet count < 20 x 10^9/l	Platelet count ≥ 20 x 10^9/l	Platelet count < 20 x 10^9/l
Non-randomized studies												
Wassenaar 2008[24]	Control group Retro-spective database analysis	30	17	NR	30 APL (No comparison made between those that received/did not receive EACA)	Chemo [30] (19 pre-ATRA era)	Loading dose 6g Followed by 1g/hr continuous infusion	Infusion	IV	If α-2-antiplasmin < 50%	If α-2-antiplasmin > 50% for 2 consecutive days	NR
Ballen 2004[25]	No control group	26	26	NR	14 Lymphoma 8 MM 4 Solid tumors	AutoSCT [26]	1 to 6g titrated upwards to treat bleeding Max dose 24g/day	4 x /day	PO IV infusion if unable to tolerate PO	Platelet count < 30 x 10^9/l	When thrombocyto penia had resolved	25/26 had none (religious reasons)
Bartholom ew 1989[[26]44]	No control group	17	17	17	8 ITP 2 MDS & ITP 2 HIV 1 AA 1 CLL 1 Drug induced thrombocytope nia 1 BSS 1 Unknown	NR	Loading dose 5g Then 1g	6 x /day. Decreased to 4x /day once bleeding stopped	14/17 PO 3/17 IV	To control bleeding. 3/14 had platelet count > 20 x 10^9/l prior to Rx	Platelet count 35 to 50 x 10^9/l	NR
Benson 1993[27]	No control group Retro-spective	18	18	9	6 Solid tumors 3 CML 3 AML 2 ALL 4 Other	Auto SCT [8] AlloSCT [10]	0.5 to 1.5g/hr	Infusion	IV	To control severe bleeding	NR	NR
Brown 2006[28]	No control group	48	48	NR	23 MM 15 NHL 8 HL 2 Solid tumors	AutoSCT [48]	4g	6x /day	IV	Platelet count < 30 x 10^9/l	NR	None (religious reasons)

Table 3.
Continued

Study	Type of study	No. of pts	No. who rec'd EACA	No. platelet refractory/ allo-immunization	Diagnosis of patient	Treatment of underlying disease	EACA dose	EACA frequency	EACA route	Treatment started	Treatment stopped	Platelets given
Chakrabati 1998[29]	No control group	15	15	NR	4 AML 4 ALL 5 ITP 2 AA	NR	Major bleeding Loading dose 5g then 1g Minor bleeding 250mg	Major bleeding 4 x /day increased to 6x /day if no response 4 x /day	NR	Platelet count < 20 x 10^9/l and bleeding	NR	If no response to 6g EACA per day
Gardner 1980[30]	No control group	14 (4 Ped)	14	At least 2	9 AA 1 AML 1 ALL 1 Myelofibrosis 2 Other	NR	8 to 24g/day in adult patients	Varied. Up to 13 months of Rx.	IV or PO	To control bleeding	Platelet count > 20 x 10^9/l	Therapeutic
Garewal 1985[31]	No control group	9	9	8	4 AML 2 ALL 1 CLL 1 MDS 1 Other (Excluded APL)	NR	Loading dose 5g Then 4g	6 x /day (decreased to 3 to 4 x/day if higher dose not tolerated)	IV or PO	Platelet count < 20 x 10^9/l	NR	NR
Kalmadi 2006[11]	Retro-spective database analysis of patients receiving EACA Only pts > 18yrs & plt count < 75 x 10^9/l No control group	77	77	32	22 AML 20 MDS (11 transforming to AML) 10 NHL 6 CML 4 ALL 2 AA 2 ITP 2 Myelofibrosis 1 CLL 1 MM 7 Solid tumors	NR	Median initial dose 4g/day (range 2g to 24g/day). Median dose 6g/day (range 2g to 24g/day).	NR	NR	Median plt count 7 x 10^9/l (range 1 to 66 x 10^9/l).	Median duration of treatment 8 days (range 1 to 216 days)	NR

AA = aplastic anemia
AlloSCT = allogeneic stem cell transplant
AML = acute myeloid leukemia
AutoSCT = autologous stem cell transplant
ALL = acute lymphocytic leukemia
APL = acute prolymphocytic leukemia
ATRA = All Trans Retinoic Acid
BSS = Bernard Soulier Syndrome
Chemo = chemotherapy
CLL = chronic lymphocytic leukemia
CML = chronic myeloid leukemia
CNS = central nervous system
CTCAE = common toxicity criteria adverse events
GI = gastrointestinal
Hb = hemoglobin
HL = Hodgkin's lymphoma
ICH = intra-cranial hemorrhage
ITP = immune thrombocytopenia
IV = intravenous
MDS = myelodysplastic syndrome
MM = Multiple myeloma
Mth = month
NHL = non-Hodgkin's lymphoma
NR = not reported
Ped = pediatric
Plt = platelet
PO = oral
Pt = patient
RBC = red blood cell
Rx = treatment
Tx = transfusion
VTE = venous thromboembolism

Table 4: Epsilon Aminocaproic Acid Studies (Results)

Study	Type of study	No. of pts	Diagnosis of patient	Thrombotic risk	Bleeding	Death due to bleeding	Platelet transfusions	Platelets given
Randomized studies								
Gallardo 1983[23]	RCT	19	15 AML 4 ALL	No deaths due to thromboembolic disease	Capillary bleeding EACA 31% of days at risk* Placebo 50% of days at risk* Major bleeding† EACA 15% Placebo 19%	NR	EACA 1 every 13.3 days at risk* Placebo 1 every 10.5 days at risk*	Prophylactic
Non-randomized studies								
Wassenaar 2008[24]	Control group	30	30 APL	1 episode of catheter assoc. thromboembolism. No effort to identify asymptomatic episodes of VTE	No CTCAE grade 4 bleeding Grade 3 bleeding [9] Grade 2 bleeding [3] Grade 1 bleeding [5]	None	NR	NR
Ballen 2004[25]	No control group	26	14 Lymphoma 8 MM 4 Solid tumors	NR	5/26 bled 2 life-threatening (1 died) 1 nasal packing 2 minor No bleeding when plt count > 5 x 10^9/l	1 Died ICH (D7) CNS disease (medulloblastoma)	1 patient with ICH	25/26 had none (religious reasons)
Bartholomew 1989[26]	No control group	17	8 ITP 2 MDS & ITP 2 HIV 1 AA 1 CLL 1 Drug induced thrombocytopenia 1 BSS 1 Unknown	NR	All bled prior to EACA. 1/17 Bleeding stopped 16/17 Bleeding controlled	1 Died ICH (ICH present prior to EACA administration)	Platelet use decreased from 164 units in 8/12 period prior to EACA to 18 units in 4/12 period following administration of drug	NR
Benson 1993[27]	No control group	18	6 Solid tumors 3 CML 3 AML 2 ALL 4 Other	No thrombotic events	Bleeding markedly reduced/stopped 12/18 No response 6/18	NR	NR	NR
Brown 2006[28]	No control group	48	23 MM 15 NHL 8 HL 2 Solid tumors	NR	1 Major GI bleed	None	None	None (religious reasons)
Chakrabati 1998[29]	No control group	15	4 AML 4 ALL 5 ITP 2 AA	NR	Prior to EACA 10/15 had major bleeding and 5/15 minor bleeding. During EACA 8/10 with major bleeding stopped bleeding 2/10 stable Hb. 5/5 with minor	None	NR	If no response to 6g EACA per day

					bleeding stopped bleeding			
Study	**Type of study**	**No. of pts**	**Diagnosis of patient**	**Thrombotic risk**	**Bleeding**	**Death due to bleeding**	**Platelet transfusions**	**Platelets given**
Chakrabati 1998[29]	No control group	15	4 AML 4 ALL 5 ITP 2 AA	NR	Prior to EACA 10/15 had major bleeding and 5/15 minor bleeding. During EACA 8/10 with major bleeding stopped bleeding 2/10 stable Hb. 5/5 with minor bleeding stopped bleeding	None	NR	If no response to 6g EACA per day
Gardner 1980[30]	No control group	13	9 AA 1 AML 1 ALL 1 Myelofibrosis 1 Other	No thromboembolic events observed	Not reported for all patients. Text reports decreased bleeding	None	Platelet usage reported for 4/13 receiving long term EACA (> 5 mths). Before EACA 30units plts/pt/mth During EACA 1unit plts/pt/mth	Therapeutic
Garewal 1985[31]	No control group	9	4 AML 2 ALL 1 CLL 1 MDS 1 Other	No thromboembolic events observed	All bled prior to EACA. 3 bled during EACA	2 Died ICH (D8; D21) 1 Died bleeding peptic ulcer (D29) (All had progressive disease unresponsive to treatment)	NR	NR
Kalmadi 2006[11]	Retrospective database analysis No control group	77	22 AML 20 MDS (11 transforming to AML) 10 NHL 6 CML 4 ALL 2 AA 2 ITP 2 Myelofibrosis 1 CLL 1 MM 7 Solid tumors	NR	51 bleeding stopped 13 reduced RBC requirements by > 50% compared to previous 3/7 13 no response	NR	Before EACA mean 1.5 ± 0.8 plt Tx/day During EACA mean 1.0 ± 0.7 plt Tx/day (P < 0.0001 t test)	NR

* Days at risk defined as days when platelet count less than 20 x 10^9/l

† Major bleeding defined as nose bleeding requiring posterior packing, gross gastrointestinal or genitourinary tract bleeding and central nervous system bleeding

NR = not reported

Table 5: Prophylactic use of Tranexamic acid vs. Epsilon Aminocaproic Acid in RCTs. Organized in order of increasing ratios TXA vs. EACA. (Data from Henry et al 2011[8]).

Study	Number of participants		Study group	Dose Assume median weight 80kg (PLADO data)			Effect	
	TXA	EACA		TXA	EACA	Ratio	Blood loss (mls). Random mean difference	Exposure to blood
Dalmau 2000[32]	42	42	Orthotopic liver transplantation	16mg/kg/hr	16mg/kg/hr	1:1	Not reported	Not reported
Dalmau 1999[33]	42	42	Orthotopic liver transplantation	10mg/kg/hr	16mg/kg/hr	1.6:1	Not reported	No difference. Trend to TXA 0.81 (0.64 to 1.02)
Fergusson 2008[34]	770	780	High risk cardiac surgery patients	30mg/kg loading dose 16mg/kg maintenance 2mg/kg bypass circuit TOTAL = 3.84g	10g loading dose and 2g maintenance TOTAL = 12g	3.125:1	Not reported	No difference 1.0 (0.93 to 1.07)
Camarasa 2006[35]	35	32	Total knee replacement	10mg/kg over 30mins followed by 10mg/kg for 3 hrs TOTAL = 3.2g	100mg/kg over 30mins followed by 1g/hr for 3hrs TOTAL = 11g	3.44:1	No difference. -9 (-270.16 to 252.16)	No difference. Trend to TXA 0.23 (0.03 to 1.94)
Casati 1999[36]	72	68	Cardiac surgery (assume 3.5 hr op)	1g over 20 mins followed by 400mg/hr and 500mg pump prime	5g over 20mins followed by 2g/hr and 2.5g added to pump prime	5:1	Favours TXA. -156.00 (-234.25 to -77.75)	No difference 0.7 (0.41 to 1.18)
Menichetti 1996[37]	24	24	Cardiac surgery (assume 3.5hr op)	10mg/kg bolus then 3mg/kg/hr. Additional 10mg/kg to prime TOTAL = 2.44g	80mg bolus, 30mg/kg/hr. Additional 80mg/kg to prime TOTAL = 14.88g	6:1	Favours EACA. 225.0 (36.28 to 413.72)	Favours EACA
Maineri 2000[38]	24	24	Cardiac surgery (assume 3.5 hr op)	20mg/kg over 60 mins then 2mg/kg/hr TOTAL = 2g	10g over 30mins followed by 2g/hr TOTAL = 16g	8:1	No difference. -40 (-206.73 to 126.73)	No difference
Landymore 1997[39]	56	44	Cardiac surgery (assume 3.5 hr op)	10mg/kg/hr followed by 1mg/kg/hr TOTAL = 1.08g	5g followed by 1g/hr TOTAL = 8.5g	8.5:1	Favours EACA/ 192 (65.87 to 318.13)	Not reported
Pinosky 1997[40]	20	20	Cardiac surgery	15mg/kg followed by 1mg/kg/hr for 6 hrs TOTAL = 1.68g	150mg/kg/hr followed by 10mg/kg/hr for 6 hrs TOTAL = 16.8g	10:1	Favours TXA. -361 (-666.56 to -55.4)	No difference. Trend to EACA 1.57 (0.77 to 3.22)
Penta de Peppo 1995[41]	15	15	Cardiac surgery	10mg/kg followed by 1mg/kg for 10hr TOTAL = 1.6g	10g followed by 2g/hr for 5 hrs TOTAL = 20g	12.5:1	No difference. 25 (-138.86 to 188.86)	No difference. Trend to TXA 0.33 (0.04 to 2.85)

Figure 1: Fergusson Trial 2008 (BART trial). Comparison of outcomes between TXA and EACA

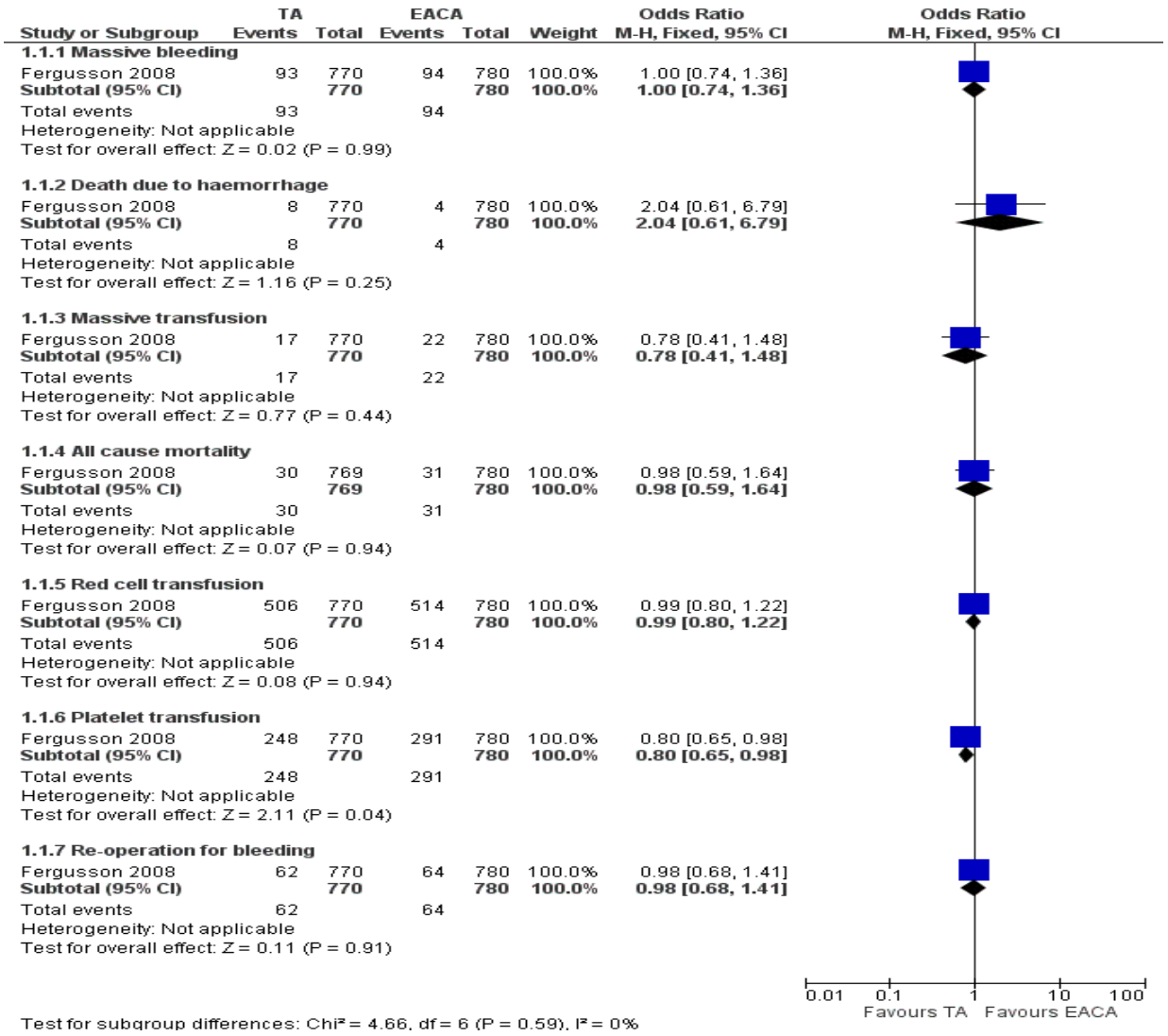
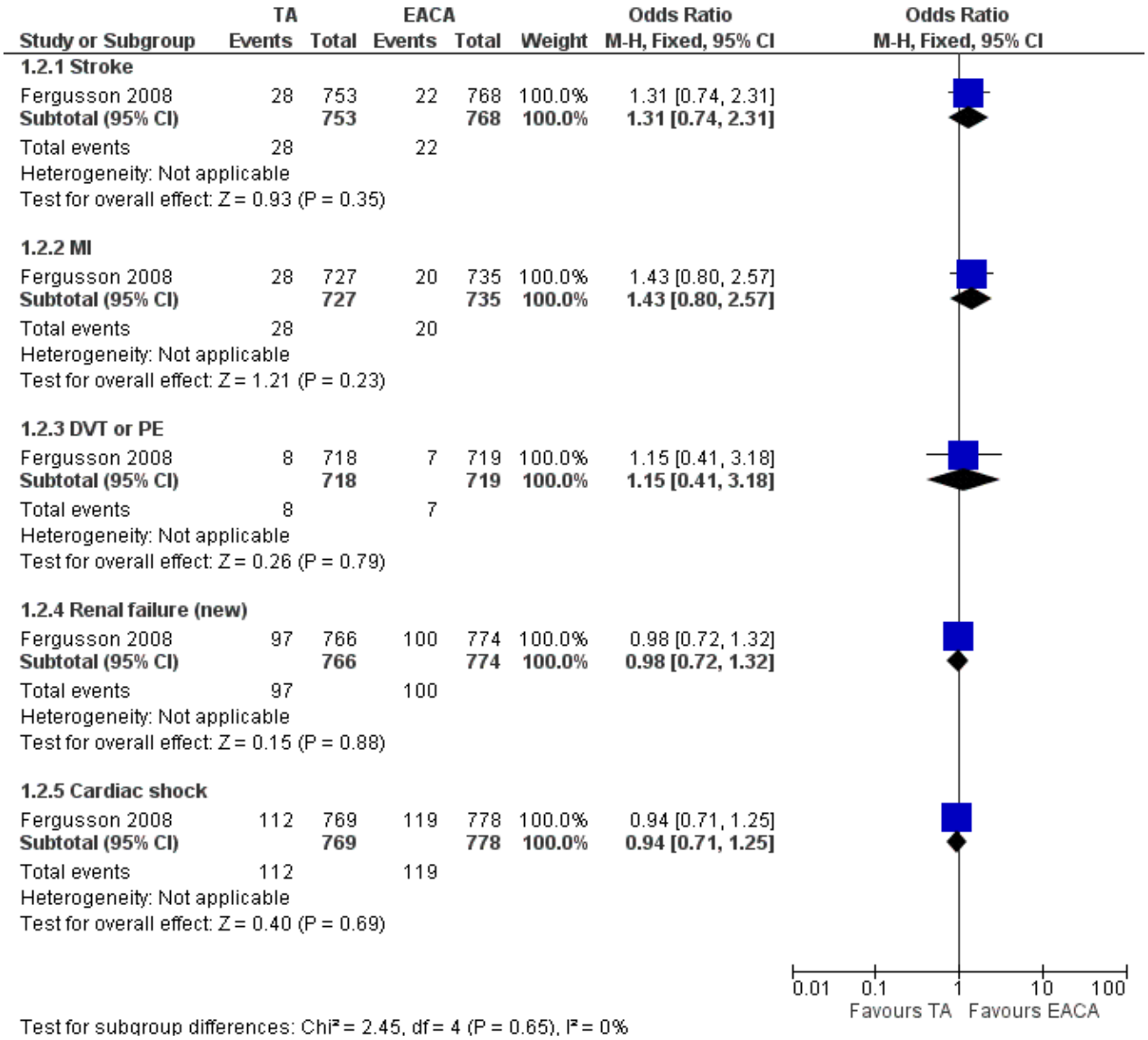


Figure 2: Fergusson Trial 2008 (BART). Comparison of adverse events between TXA and EACA.



APPENDIX 2: WHO GRADING SYSTEM

General Definitions of WHO Grades

Grade 1 Any bleeding that does not fulfil the criteria for Grade 2 bleeding (general or organ-specific). For examples of grade 1 bleeding, please see organ-specific definitions.

Grade 2 Any bleeding that does not fulfil the criteria for Grade 3 bleeding (general or organ-specific) BUT requires an intervention or treatment:

- Examples of interventions
  - Nasal packing
  - Bladder irrigation
- Examples of treatments
  - Platelet transfusion given to treat active bleeding and NOT given only because the platelet count is below the prophylactic platelet transfusion trigger
  - Medications prescribed to treat bleeding

Grade 3 Any bleeding that does not fulfil the criteria for Grade 4 bleeding (general or organ-specific) BUT requires:

- Red cell transfusion specifically related to treatment of bleeding within 24 hours of onset of bleeding, for example:
  - Required to treat fall in hemoglobin of at least 2 g/dL within preceding 24 hours without evidence of hemolysis
  - No hemoglobin increment within 24 hours of at least a 2 unit red cell transfusion without evidence of hemolysis
- A significant intervention, for example:
  - Endoscopy to treat the bleeding
  - Interventional radiography to treat the bleeding
  - Transfer to the operating room for treatment of bleeding

Grade 4 Any bleeding that is:

- Fatal
- Life-threatening. For example:
  - Bleeding that requires transfer to intensive care/treatment unit
  - Bleeding that is associated with hemodynamic instability and causes inadequate tissue perfusion, including:
    - Hypotension
      - Systolic blood pressure (BP) < 90 mmHg
      - > 40 mmHg fall in systolic BP
      - Mean arterial pressure (MAP) < 65 mmHg
    - In absence of hypotension, markers of inadequate tissue perfusion include:
      - Increased blood lactate
      - Increased base deficit
      - Perfusion related low pH (if other causes of metabolic acidosis (e.g. sepsis) are not present)

Organ-specific definitions of WHO Grades

	Grade 1	Grade 2	Grade 3	Grade 4
General	Bleeding that does not fulfil the requirements for grade 2 bleeding. Please see examples in organ-specific categories below.	Any bleeding that does not fulfil the requirements for grade 3 bleeding BUT requires an intervention or treatment: Examples of Interventions - Nasal Packing - Bladder irrigation Examples of treatments - Platelet transfusion given to treat active bleeding and NOT given only because the platelet count is below the prophylactic platelet transfusion trigger - Medications prescribed to treat bleeding	Any bleeding that does not fulfil the criteria for grade 4 bleeding BUT requires: Red cell transfusion specifically related to treatment of bleeding within 24 hours of onset of bleeding. **OR** A significant intervention, for example: - Endoscopy to treat the bleeding - Interventional radiography to treat the bleeding - Transfer to the operating theatre/ room for treatment of bleeding	Any bleeding that is fatal or life threatening. For example: - Bleeding that requires transfer to intensive care/treatment unit - Bleeding that is associated with hemodynamic instability and causes inadequate tissue perfusion (for further clarification see general guideline above).
Oral and nasal†	Spontaneous oropharyngeal bleeding - total duration of all episodes in previous 24 hours < 30 minutes* Traumatic oropharyngeal bleeding e.g. after bites to lips and tongue lasting > 10 minutes or interfering with daily activities Epistaxis - total duration of all episodes in previous 24 hours < 30 minutes* Petechiae of oral mucosa Few (≤ 5) hemorrhagic bullae or blisters	Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes* Multiple (> 5) hemorrhagic bullae or blisters	Any bleeding that requires a transfusion or a procedure (not including intubation)	Any bleeding that requires intubation to protect the airway
Skin†	Few (≤ 5) spontaneous bruises (ecchymoses) over 2.5cm in size and none >10cm Purpura (3mm to 10mm diameter) (Few purpuric lesions	Multiple (> 5) spontaneous bruises (ecchymoses) each >2.5cm or any one >10cm. Many (> 10) spontaneous bruises (ecchymoses) (>10mm in diameter) that does not fulfil the above criteria. Purpura (3mm to 10mm	Any bleeding that requires a transfusion or a procedure	

	(≤ 10). Petechiae (< 3mm diameter) covering ≤ 25% of skin (1 arm = 10%; 1 leg = 25%; trunk = 44%; head = 6%)	diameter). Many purpuric lesions (> 10). Petechiae covering > 25% of skin (1 arm = 10%; 1 leg = 25%; trunk = 44%; head = 6%).		
Soft-tissue and musculoskeletal	Asymptomatic spontaneous soft-tissue hematoma less than 10cm in diameter. Traumatic joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	Asymptomatic spontaneous soft-tissue hematoma greater than 10cm in diameter. Symptomatic soft-tissue hematoma (e.g. causing pain or discomfort). Spontaneous joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	Any bleeding that requires a transfusion or a procedure (not including compartment syndrome)	Any bleeding that causes compartment syndrome.
Gastrointestinal	Fecal occult blood Rectorrhagia- visible red blood on tissue paper/not mixed with stool	Melena Hematochezia – visible red blood mixed in stool, not requiring a transfusion Hematemesis – Grossly visible blood in emesis (vomit) or in nasogastric drainage tube (not related or secondary to swallowed blood)	Rectal Bleeding requiring a transfusion Hematemesis requiring a transfusion Any bleeding that requires a transfusion or a procedure	
Genitourinary	Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle OR Bleeding heavier than normal OR Breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting Gross/visible hematuria	Any bleeding that causes: increase ≥1.5 X reference serum creatinine‡ or Serum creatinine rises by ≥ 26µmol/L (0.3mg/dl) within 48 hours or Urine output <0.5 mL/kg/hr for > 6 consecutive hrs Or Any bleeding that requires a transfusion or a procedure	Any bleeding that causes: increase ≥3 X reference serum creatinine‡ or Serum creatinine rises by ≥354 µmol/L (4.0 mg/dl) or Commenced on renal replacement therapy or Urine output <0.3 mL/kg/ hr for > 24 hrs or Anuria for at least 12 hrs
Pulmonary		Hemoptysis – Visible blood	Any bleeding requiring supplemental oxygen to maintain	Any bleeding requiring respiratory support (includes

		Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding or mucositis).	oxygen saturation above 93%.	non-invasive (CPAP, BiPAP), or invasive ventilation)
Body cavity		Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	Grossly visible blood in body cavity fluids AND organ dysfunction with symptoms, AND/OR need to intervene (e.g. to aspirate). Any bleeding that requires a transfusion or a procedure	
Eye†	Sub-conjunctival hemorrhage Traumatic retinal bleeding without visual impairment Traumatic vitreous bleeding without visual impairment	Diffuse sub-conjunctival hemorrhage in both eyes Spontaneous retinal bleeding without visual impairment Spontaneous vitreous bleeding without visual impairment	 Retinal bleeding with temporary visual impairment ** (present for ≤ 7 days) Vitreous bleeding with temporary visual impairment *** (present for ≤ 7 days)	 Retinal bleeding with permanent visual impairment ** (present for > 7 days) Vitreous bleeding with permanent visual impairment ** (present for > 7 days)
Central nervous system		Lumbar puncture with blood (>5 RBC/µL in CSF on microscopic analysis and non-traumatic tap), no neurological symptoms and no visible red color Traumatic CNS bleeding on imaging study without neurological dysfunction	Lumbar puncture with visible red color in absence of neurological symptoms, and non-traumatic tap Spontaneous CNS bleeding on imaging study without neurological dysfunction	CNS symptoms with non-traumatic bloody lumbar puncture CNS bleeding on imaging study with neurological dysfunction
Invasive sites	Bleeding at invasive sites or sites of minor trauma (e.g. venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for > 10 minutes	Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours.	Any bleeding that requires a transfusion or a procedure	

*Count actual bleeding (i.e. “running out” or need for basin, tissue, towel, etc.) not minor bleeding
**Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmological consultation
*** Visual impairment confirmed by ophthalmological consultation
† Petechiae of oral mucosa and skin
Subconjunctival hemorrhage
Hemorrhagic bullae/blisters in mouth
Purpura and ecchymoses
These are all documented as bleeding on the 1st day they are seen and any subsequent day that the bleeding is worse than the preceding day. If the bruising / petechiae is the same as or not as severe as the previous day it will not be counted as bleeding [For discussion].

‡ Reference serum creatinine is the baseline serum creatinine result taken on entry into the study

Definitions of Bleeding Signs

Definition of bleeding signs based on physical examination		
Site of bleeding	**Sign**	**Definition**
Skin (epidermis and dermis)		
	Petechiae	Red (recent) or purplish (a few days old) spot discoloration in the skin with a diameter between 0.5 mm to < 3 mm, not blanching with pressure and not palpable
	Purpuric macule (purpura)	Differentiated from petechiae only for their larger size between 3 to 10 mm.
	Ecchymosis (bruise or contusion)	Larger than 10mm in size. Flat, rounded or irregular, red, blue, purplish or yellowish green patches, larger than a petechia or purpura. If elevated they represent superficial spreading of an underlying hematoma
Skin (subcutaneous tissue)		
	Hematoma	Bulging localized accumulation of blood often with discoloration of overlying skin
Visible mucous membranes		
	Petechia, purpuric macules and ecchymoses	As for skin
	Bulla/vesicle (Blister)	Visible raised, thin-walled, circumscribed lesions containing blood. Bullae (≥ 5mm) are larger than vesicles (< 5 mm). They should be counted together as bullae
	Epistaxis	Any bleeding from the nose, may be anterior or posterior and unilateral or bilateral
	Gingival bleeding	Any bleeding from the gingival margins
	Subconjunctival hemorrhage	Bright red discoloration underneath the conjunctiva at onset then same color changes as ecchymoses
Muscles and soft tissues		
	Hematoma	Any localized collection of blood, visible or palpable or revealed by imaging. May be dissecting when spreading along fascial spaces

Appendix 3: A-TREAT Telephone Script: Long-Term Follow-Up

To be performed at 30 days post discontinuation of study drug & 120 days post activation of study drug

Assessment Time Point:

- ☐ 30 days post discontinuation of study drug
- ☐ 120 days post activation of study drug

☐ No answer/patient unavailable:

- ☐ No voicemail/message left- local physician will be contacted for medical records
- ☐ Left voicemail/message:_____

☐ Made contact with patient:

Recommended Introduction: My name is [*name of CRC, Research Nurse or Investigator*] and I am calling from [*study site*] for a quick follow up regarding the A-TREAT clinical trial you recently participated in. I have a few questions to ask that will help our team understand how you're doing after treatment:

- How are you feeling?
- Have you experienced any health problems since the last time someone from the study team spoke with you?
- Have you experienced, or are you currently experiencing, any of the following:

☐ swelling in your arms or legs
Comment:_____

☐ shortness of breath
Comment:_____

D30 Patient Reminders and Recommended Closing Comments: Just a reminder that we will call for your last study follow-up on [*date of D120*]. Thank you for your time and further participation, please don't hesitate to contact us at [*phone number, email address, clinic name*] if you have any questions or concerns regarding the study.

D120 Recommended Closing Comments: Thank you for your participation in this study- today was the last scheduled follow-up, but please feel free to contact us at [*phone number, email address, clinic name*] with any quesitons or concerns regarding the study.

Signature: Date and Time of Call:

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