# Clinical Research Manual of Operations

**Purpose:** The Clinical Research Manual of Operations (CMOO) details the ATREAT clinical study procedures not covered in the Data Forms Manual of Operations (MOO).

### 1) Study Protocol and data forms Manual of Operations

The study protocol is FDA, DSMB, NHLBI, and IRB approved, outlines how the study is to be conducted, and who the Principal Investigators are at each clinical site. The data forms MOO details information needed to enter subject information into the data base.

### 2) Study Flow Diagram

See Section 1, Page 12 of study protocol for the study flow diagram.

### 3) Staff Roster

Clinical Coordinating Center
Terry Gernsheimer, MD, Director
Seattle, WA 98195-6330

Data Coordinating Center
Susanne May, PhD, Director
Seattle, WA 98115

## 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 |
| **CCC** | Central Coordinating Center |

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|---|---|
| **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 |
| **HIPAA** | Health Information Privacy and Affordability Act |
| **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 or Research Nurse |
| **RC** | Research Coordinator |
| **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 |

## D) Trial Organization and Responsibilities

**The A-TREAT web site**: https://a-treat.uwctc.org/registered-home/
The web site contains information on organization, committee agendas, committee minutes, Clinicaltrials.gov registry, events calendar, announcements, protocols, ICs, Data Forms, the database, clinical and pharmacy MOOs, training information, DSMB, and other study information as requested by the Steering Committee.

**The Steering Committee**: The Chair is the CCC PI and membership consists of the PIs of each site, DCC PI, and study representatives from the NHLBI. They meet every 2nd and 4th Monday of the month at 07:00 PT (10:00 ET) by conference call.

Objective: The Steering Committee is the overall governing body of A-TREAT. It is ultimately responsible for all aspects of the study including protocol development and implementation as well as publication of study results. The Steering Committee meets by conference call bi-weekly. This group consists of the Chair (Gernsheimer), the PI from each site. the DCC PI (May) and the NIH. Each site has one vote and the DCC has one vote. The NIH has a vote in the case of a tie. Others may attend the calls as needed (study coordinators, co-investigators, etc.).

**The Study Monitoring Committee**: meets every 1st and 3rd Monday of the month. The Chair is the PI at the DCC, and members include the PI at each enrolling site and the DCC. The committee is primarily responsible for reviewing the conduct of the study with respect to quality assurance of protocol implementation and data collection. The activities of the SMC will include:

1. Proposing the standards for acceptable adherence to protocols and data collection/data entry. These standards will include the criteria used to measure adherence, as well as the thresholds indicating a need for further investigation.
2. Development of reports on site performance for use in identifying areas of concern. These reports will be developed in conjunction with the DCC.
3. Review of the reports of study progress and site performance on at least a monthly basis, with more frequent monitoring as needed
4. Interacting with the sites as necessary to develop plans for addressing any particular areas of concern
5. Reporting to the Steering Committee on study progress, adherence to study protocols, and adherence to standards for data completeness, timeliness, and quality.

**The RN/Coordinator Committee** The Chair is the RN/RC designated by the PI at the CCC, and members consist of Research Nurses (RNs) and Research Coordinators (RCs) from each site and the DCC. They meet every Tuesday at 10:00 PT (13:00 ET) by conference call.

Objective: The objective of the Coordinator's Committee is to collaborate and share information and resources in order to facilitate both the general goals of A-TREAT as well as those related to protocol implementation. The coordinators meet in conjunction with but separate from the general Steering Committee meeting in order to discuss relevant topics such as protocol implementation and adherence, data collection, patient consent and follow-up, IRB issues, staffing, etc. The chair is Rachel DeWitt from the CCC. Heather Herren at the DCC backs her up.

**The Pharmacy Committee** The Chair is the head IDS pharmacist at the CCC and membership consists of Investigational Drug Services pharmacists from each site, the main coordinator from each study site and a DCC representative. They meet as needed.

Objective: This committee develops processes for ordering, receiving and administering the study drugs, and maintains study drug records. The pharmacists on this committee are un-blinded.

**The Data Safety and Monitoring Board** is an independent body that provides recommendations to the Office of the Director, NHLBI, and is required to provide recommendations about starting, continuing, and stopping the study. They meet approximately every 6 months after initial protocol approval.

Objective: The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, ensuring data quality, and for monitoring the overall conduct of the studies. For each of the clinical trials in its portfolio the DSMB is expected to evaluate candidate protocols for safety and equipoise, and monitor ongoing studies to ensure compliance with protocols, accurate and timely reporting of adverse events, and acceptable subject recruitment rates. In performance of these duties the DSMB may elect to review un-blinded study data and/or request detailed information from the study Sponsor or Principal Investigator(s).

**The Clinical Trial Synchronization Committee** is charged with communicating and synchronizing the US and UK TXA studies. The Clinical Trial Synchronization Committee meets monthly by conference call. Chairs will be Gernsheimer and Stanworth (UK Trial PI). Members include the Chairs, the statistician at the UK site, and the PI at the DCC, Susanne May.

**The Publication Committee** objective is to assure that substantive A-TREAT findings are accurately presented and published in a timely manner in peer-reviewed journals. The Committee will review and must approve all abstracts, presentation and manuscripts prior to submission or presentation. Finally, the Committee is responsible for resolving any authorship disputes that cannot be resolved within the writing group. Meeting

frequency at least once yearly after enrollment begins. The Chair is the PI at the CCC. Members include the PI at each enrolling site and the DCC.

## TABLE OF TASKS WITH ASSOCIATED RESPONSIBLE UNIT

**NHLBI OVERSIGHT –** NHLBI
**TRIAL STEERING CMTE –**Dr. Gernsheimer is the Chair. Members include representatives of the CCC (Gernsheimer), DCC PI (May), each site PI and NIH.
**CLINICAL CORE –** This group will be headed by Dr. Gernsheimer and fill the role of Clinical Coordinating Center (CCC).
**STAT/DATA CORE –** This group will be headed by Dr. May and fill the role of Data Coordinating Center (DCC).
**CLINICAL SITE –** This represents each of the clinical sites selected for the trial.
**DSMB –** This group is selected by the NHLBI and will review the IRB protocol to satisfy the scientific review requirement.

| **TASK** | **DESCRIPTION** | ***RESPONSIBILITY*** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| *I. ADMINISTRATIVE ORGANIZATION* | | | | | | | | |
| **I. Pre-Study Steering Committee, Stat/Data Core, meetings/teleconferences**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Arrange meetings/teleconferences | | | | P | | | |
| | Chair the meetings/teleconferences | | | | P | | | |
| | Attend meetings/teleconferences | | P | P | P | P | | |
| | Write and distribute draft minutes | | | | P | | | |
| | Review and comment on draft minutes | | P | P | P | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Distribute final minutes | | | | P | | | |
| **II. Steering Committee meetings/teleconferences**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Arrange meetings/teleconferences | | | | P | | | |
| | PI of CCC to chair meetings/teleconferences | | | | P | | | |
| | Attend meetings/teleconferences | | P | P | P | P | | |
| | Write and distribute minutes | | | | P | | | |
| | Review and comment on draft minutes | | | P | P | P | | |
| | Distribute final minutes | | | | | P | | |
| **III. Stat/Data Committee meetings/teleconferences** | | | | | | | | |
| | Arrange meetings/teleconferences | | | | | P | | |
| | PI of Stat/Data Core to chair meetings/teleconferences | | | | | P | | |
| | Attend meetings/teleconferences | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| **IV. DSMB meetings/teleconferences**<br>**TABLE KEY**<br>**P = Primary responsibility for the completion of the task**<br>**O = Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility**<br>**R = Review and approval of materials** | | | | | | | | |
| | Arrange meetings/teleconferences | | | | | P | | |
| | Attend meetings/teleconferences | | P | | P | P | | P |
| | Receive DSMB recommendations | | P | | | | | |
| | Respond to DSMB recommendations | | | P | | | | |
| *II. PLANNING* | | | | | | | | |
| **A. Protocol Development** | | | | | | | | |
| | Develop and refine, protocol | | O | P | P | P | | |
| | Produce protocols (track protocol changes) | | | | P | | | R |
| | Develop model informed consent | | O | R | P | | | R |
| | Modify model consent statement to include Clinical Site specific language | | | | R | | P | R |
| **B. Regulatory Affairs Activities** | | | | | | | | |
| | FDA-IND submission | | | | | P | | |
| | Submit protocol and all amendments to the FDA | | | | | P | | |
| | Maintain clinical trial dossier | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DSMB** |
| | Submit interim and final reports to FDA as required by FDA contacts if applicable | | | | | P | | |
| | Register and maintain on www.clinicaltrials.gov | | | | | P | | |
| **C. Study Preparation**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Develop a project implementation timetable and work plan. | | O | P | | | | |
| | Determine regulatory documents required from sites. | | | | | P | P | |
| | Collect regulatory documents required from sites. | | | | | P | | |
| | Clinical Sites to send in required regulatory documents as requested by the DCC | | | | | R | P | |
| | Develop public and internal websites | | | | R | P | | |
| | Provide sites with up-to-date Investigator's Brochure (IB) and/or product inserts. | | | | P | | | |
| | Establish external, independent Data and Safety Monitoring Board (DSMB). | | P | | | | | |
| | Prepare the full charter document for the DSMB outlining their responsibilities, based on the Steering Committee's recommendations | | P | R | R | R | | R |
| | Determine DSMB monitoring plan and reporting rules for the DSMB for safety and/or efficacy. | | R | R | R | P | | P |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DSMB** |
| | Develop computer programs to produce safety and efficacy reports, data quality reports, as well as enrollment/activity reports for DSMB meetings, with input from the Steering Committee. | | R | R | | P | | |
| | The DSMB open minutes will be distributed by the CCC to the Clinical Sites for submission to the site's IRBs | | | | | P | | |
| | Modify interactive electronic incident reporting modules to receive and convey telephone reports of events that must be tracked in real time (e.g., serious adverse events, dose adjustments, subject terminations, and drug disclosures). | | | R | R | P | | |
| | Review/refine procedures for reporting serious adverse experiences to DCC, DSMB, FDA, and the clinical sites. | | O | R | P | P | R | |
| | Develop randomization scheme. | | | | | P | | |
| | Create programs and validate all programs for the randomization scheme. | | | | | P | | |
| | Develop on-line enrollment module that will incorporate randomization there for assignment of participant. | | | | R | P | | |
| | Modify computerized enrollment module for recording, tracking, and reporting study enrollment in real-time. | | | | R | P | | |
| **D. Development and Distribution of Case Report Forms (CRFs)**<br>**TABLE KEY**<br>P = Primary responsibility for the completion of the task<br>O = Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>R = Review and approval of materials | | | | | | | | |
| | Develop the content and design of the study's case report forms. | | O | R | P | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Develop a schedule of assessments by task and by data form. | | O | R | P | R | | |
| | Train site personnel on electronic data entry of CRFs | | | | | P | | |
| ***F. Site Monitoring*** | | | | | | | | |
| **TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Develop a site monitoring plan. | | | R | P | P | | |
| | Identify primary safety and efficacy variables that will require source document review. | | | P | R | P | | |
| | Identify monitor(s). | | | | | P | | |
| ***G. Operations Manual*** | | | | | | | | |
| | Compose a detailed Operations Manual for multi-arm transfusion study. Sections to be included are: Section I – Study Protocol; Section II – Enrollment; Section III – Protocol Visits; Section IV – Case Report Forms; Section V – Pharmacy Policies; Section VI – Adverse Events; Section VII – Dosing Procedures; Section VIII – Laboratory Procedures; Section IX – Assessments; Section X – Site Monitoring; Appendices; List of Tables; List of Figures; List of Sample Documents. | | | R | P | P | | |
| | Make copies of the Operations Manual electronically available to site investigators, coordinators electronically, CCC project team members, Stat/Data Core, and Steering Committee. | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| ***I. Data Management Plan*** <br> **TABLE KEY** <br> **P =** Primary responsibility for the completion of the task <br> **O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility <br> **R =** Review and approval of materials | | | | | | | | |
| | Develop draft Data Management Plan | | | R | R | P | | |
| | Finalize Data Management Plan | | | R | R | P | | |
| | Develop CRF/data modules. | | | | R | P | | |
| | Design CRF/correction flow. | | | | R | P | | |
| | Determine data dictionary and coding details. | | | | R | P | | |
| | Determine data editing (range checks) specifications. | | | | P | P | | |
| | Data entry verification. | | | | | P | | |
| | Develop plans for data transfer, archiving of databases and programs. | | | | R | P | | |
| | Develop data audit plans including sampling methodology and acceptable error rates | | | | R | P | | |
| **J. Statistical Analysis Plan and Publication Policy** | | | | | | | | |
| | Formulate Statistical Analysis Plan. | | O | R | R | P | | |
| | Output programming specification (Tables). | | | R | R | P | | |
| | Transfer and archiving of analysis databases and programming. | | | | R | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Develop a publication policy that clearly delineates publication plans/procedures for all primary manuscripts as well as any secondary, tertiary manuscripts. | | | P | R | R | | |
| | Type and refine publication policy. | | | R | P | R | | |
| ***K. Finance and Administration*** <br> **TABLE KEY** <br> **P =** Primary responsibility for the completion of the task <br> **O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility <br> **R =** Review and approval of materials | | | | | | | | |
| | Develop the final budget for the planning and implementation phases of the study, including the per subject budget for participating clinical centers. | | | | P | | | |
| | Finalize contracts with clinical centers. | | | | P | | | |
| | DCC to create a "Site Performance Report" for payment procedures. This report is to include information on number of subjects enrolled per site per month since initiation and other pertinent performance measures as agreed to (e.g., number of CRFs in the database, number of outstanding queries, etc.) | | R | R | R | P | R | |
| | Develop a system of site payments, including payment schedule and invoice format. | | | | P | | | |
| | Develop plan for reducing site payments for those sites that enroll fewer than expected number of subjects. | | | P | | | | |
| | Develop plan for completely deactivating poorly performing sites per recommendations by the Steering Committee. | | | P | | | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| **L. Site Selection and Establishment**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Locate medically appropriate study sites and recruit qualified investigators as necessary. | | R | R | P | R | | |
| | Collect, review, finalize with sites, pre-study regulatory and sponsor-specific documents (e.g., IRB approval letter, approved informed consent, FWAs, FDA Form 1572, ancillary personnel form, personnel signature form, Disclosure of Conflict of Interest [FDA], etc.). Review all site consent forms prior to obtaining IRB approval. | | | R | R | P | | |
| | Establish and execute consortium contracts with clinical centers. | | | | P | | | |
| **M. Orientation Meeting Planning and Conduct** | | | | | | | | |
| | Organize a work plan for the orientation meeting. | | | R | P | | | |
| | Select meeting site. | | | R | | P | | |
| | Coordinate catering and AV needs for meeting. | | | | | P | | |
| | Communicate with sites about meeting plans. | | | | | P | | |
| | Develop an agenda and determine presenters. | | | R | P | R | | |
| | Prepare meeting materials for presentation. | | | P | P | P | | |
| | Conduct meeting to orient investigators to study drug and all aspects of the study protocol. | | | P | P | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Write and distribute minutes | | | | P | | | |
| | Conduct initial and ongoing conference call(s) to orient coordinators and monitors (detailed review of protocol procedures and schedule of activities, detailed review of CRF, procedures for collection, handling, storing and shipping lab specimens). | | | | P | P | | |
| ***III. IMPLEMENTATION***<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| **O. Day-to-Day Study Management** | | | | | | | | |
| | Recruit Patients | | | | | | P | |
| | Enroll, treat and follow patients | | | | | | P | |
| | Oversee subject recruitment and enrollment. | | R | R | P | R | | |
| | Manage enrollment through web-based forms to verify eligibility and assign drug pack numbers. | | | | | P | | |
| | Prepare and distribute monthly enrollment projection and status reports to clinical centers, steering committee, NHLBI. | | | | | P | | |
| | Advise sites with slow enrollment. | | R | R | P | R | | |
| | Assist poorly performing sites in an effort to enhance performance. | | | R | P | R | | |
| | Deactivate poorly performing sites that do not significantly improve performance after receiving assistance from the CTCC. | | R | P | P | | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Administer contractual payments to clinical centers. | | | | P | | | |
| | Receive all questions from study sites, e.g., concerning protocol, SAEs, monitoring visit schedule, approval of non-protocol laboratory tests, laboratory supply problems, etc. | | | | P | P | | |
| | Complete CRFs electronically within(TBD) working days of visit | | | | | | P | |
| | Answer data queries within (TBD) working days of receipt | | | | R | | P | |
| | Determine protocol and CRF clarifications. | | | | P | R | | |
| | Communicate with sites about protocol implementation and CRF completion via phone, fax, and mail. | | | | P | R | | |
| | Complete protocol amendments as necessary. | | O | R | P | R | R | O |
| | Update the Operations Manual as needed. | | | R | P | P | | |

***P. Study Drug***

**TABLE KEY**

1. **P =** Primary responsibility for the completion of the task
2. **O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility
3. **R =** Review and approval of materials

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Determine process to blind study drugs | | | | P | R | R | |
| | Hire compounding pharmacy to perform blinding and drug packaging, distribution, etc. | | | | P | | | |
| | Contract with compounding pharmacy | | | | P | | | |
| | Inventory control | | | | P | R | P | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | | | | | | | | |
| **Q. Study Monitoring**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | DCC Monitor(s) will conduct annual field monitoring visits to each clinical center. | | | | | P | | |
| | Monitors will adhere to the CCC monitoring SOPs and guidelines. | | | | | P | | |
| | Monitors will direct site's protocol and CRF questions to CCC as necessary. | | | | | P | | |
| | DCC Monitor(s), CCC staff and other statistical center staff will hold regularly scheduled conference calls to discuss progress of study and communicate/resolve any issues as needed thereafter. | | | | P | R | | |
| | DCC Monitor(s) will visually review a percentage (**TBD)** of CRF pages for legibility and accuracy of header information, completion of all information, and presence of appropriate signatures. | | | | | P | | |
| | DCC Monitor(s) will immediately communicate to CCC any site performance problems or general monitoring issues. | | R | | P | P | | |
| | Set up regulatory data base | | | | R | P | | |
| | DCC staff, in conjunction with monitor(s), will oversee and collect as needed all regulatory documents generated during study conduct (e.g., signed consents, IRB correspondence, FWAs or SPAs, 1572 updates, etc.). | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | DCC Monitor(s) will oversee the receipt, proper storage, proper dispensing, and destruction of clinical supplies using whatever documentation is required. | | | | | P | | |
| | DCC Monitor(s) will perform source document verification of primary outcome measures and safety data. | | | | | P | | |
| | DCC Monitor(s) will validate error reports from DCC against corrected CRFs and assist clinical sites/CC in correcting reports if there are any inconsistencies. | | | | | P | | |
| | The original monitor reports will be maintained at the DCC. | | | | | P | | |
| | The DCC will ensure that any protocol deviations documented in the site visit reports are in the database by the site. If there are discrepancies between the report and the database the DCC will clarify with the site. | | | | | P | | |
| **R. Safety Monitoring**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | The Statistical Center will create blinded summary reports of aggregate safety data (e.g., AEs, lab data, concomitant meds, etc.) on a monthly basis for the PI of the CC to review as well as the Medical Monitor. | | R | | R | P | | |
| | Review on a regular basis blinded summary reports of aggregate safety data (e.g., AEs, lab data, and concomitant meds). | | R | | P | | | |
| | Report SAEs to DCC | | | | | | P | |
| | Complete SAE reports (e.g., Medwatch) | | | | R | | P | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Submit SAE reports to IRB as per each site's Institutional requirements | | | | | | P | |
| | Report submitted t SAEs to the CCC | | | | | | P | |
| | Report premature withdrawals to the DCC | | | | | | P | |
| | DCC Study coordinator will receive by phone and track via computer module real-time site contacts regarding designated serious adverse experiences, premature withdrawals (incidents). | | | | | P | | |
| | Steering Committee, NIH Oversight Committee, CC project staff, statistical staff will be sent these incidents by e-mail as soon as they are received. | | | | | P | | |
| | Information regarding SAEs will be forwarded to the Steering Committee, Statistical Center within 7 day of receipt. | | | | | P | | |
| | Information regarding SAEs will be forwarded to DSMB as outlined in the Safety Monitoring Plan. | | | | | P | | |
| | Serious unexpected suspected adverse reactions (SUSARs) need to be reported to the sites per the regulations. The Study PI will prepare a cover letter and forward safety reports to sites. | | | | P | | | |
| **S. Database Design**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | CCC and Statistical Center will collectively determine all table and variable names prior to database setup. | | | | P | P | | |
| | Create tables for maintaining CRF data based on CRF structure. | | | | R | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Create auxiliary tables utilized in the day-to-day operations of data management. | | | | R | P | | |
| **T. CRF Management**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Create study subject folders and maintain study files during study conduct. | | | | | | P | |
| | | | | | | | | |
| | Perform subject closeout procedure: Verify all forms are in subject folder; Verify subject identifiers; Perform database to CRF review; Perform other study-specific review processes. | | | | P | P | P | |
| ***U. Data Management*** | | | | | | | | |
| | Update and maintain Data Management Plan | | | | R | P | | |
| | Data Loading: Track record numbers for QA; Validate and document all software utilized in the load process. | | | | | P | | |
| | Execute error-checking software on each batch of entered data. | | | | | P | | |
| | Generate error reports for CTCC staff to communicate with monitors/sites. | | | | | P | | |
| | Communicate errors to monitors/sites via phone, fax, e-mail. | | | | | P | | |
| | Document error corrections made with sites through the monitors on CRF and error reports. | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | Update database error tracking system with corrections made with monitors and sites. | | | | | P | | |
| | Produce report of running errors for monitors and sites. | | | | R | P | | |
| | Execute update procedure to update electronic CRF data with those changes made with sites through the monitors. | | | | | P | | |
| | Validate electronic update software and document. | | | | | P | | |
| ***V. CRF Coding*** <br> **TABLE KEY** <br> **P =** Primary responsibility for the completion of the task <br> **O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility <br> **R =** Review and approval of materials | | | | | | | | |
| | Code adverse events in MEDdra or system approved by CCC. | | | | | P | | |
| ***W. Safety Labs*** | | | | | | | | |
| | Generate medical monitor reports for blinded review of serious adverse event and laboratory data on a monthly basis. | | | | | P | | |
| **X. General Reporting** | | | | | | | | |
| | Generate standard reports: <br> • Enrollment Projections by site (monthly) <br> • Activity Report (enrollments, SAEs, premature withdrawal etc.) (monthly) <br> • Site Monitoring Reports | | | | R <br> R | P <br> P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | | | | | R | P | | |
| **Y. Protocol Amendments**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | CCC will draft necessary protocol amendments | | O | R | P | R | | |
| | DCC will create a new working protocol each time an amendment is generated | | O | R | | P | | |
| **Z. Closeout Activities at the Clinical Centers** | | | | | | | | |
| | Monitors will conduct close-out visits | | | | | P | | |
| | Perform drug accountability audits | | | | | P | | |
| | Verify proper destruction of study drug at clinical center. Ensure documentation for destruction is obtained from all sites. | | | | P | P | | |
| | Collect unused non-drug study materials for proper disposal or provide clinical centers with plans for proper destruction on site. Ensure documentation for destruction is obtained from all sites. | | | | - | P | | |
| | Notify IRB when studies are completed | | | | | P | P | |
| | Notify clinical center IRB when studies are completed. Forward a copy of the letter sent to the IRB to the CTCC to maintain in the | | | | R | R | P | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DS MB** |
| | central regulatory files. | | | | | | | |
| *IV. ANALYSIS/PUBLICATION* | | | | | | | | |
| **AA. Statistical Analysis**<br>**TABLE KEY**<br>**P =** Primary responsibility for the completion of the task<br>**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility<br>**R =** Review and approval of materials | | | | | | | | |
| | Develop randomization scheme. | | | | | P | | |
| | Steering Committee and NIH Oversight Committee to agree on final analysis plan prior to unblinding. | | R | R | R | P | | R |
| | Perform interim analyses based on statistical analysis plan. | | | | | P | | |
| | Conduct data analysis for primary manuscript. Analysis to be completed **(TBD)** weeks after locked database delivered to Statistical Center. | | | | | P | | |
| | A Steering Committee member, most likely the PI of the CCC, is responsible for preparing the primary manuscripts for study. | | | P | | | | |
| | The Statistical Center will write the statistical sections for all manuscripts | | | | | P | | |
| | The Primary Author will type and refine the manuscripts | | | | P | | | |
| | Review and comment on manuscripts. | | | R | R | R | R | R |
| | Archive and comment on analysis data sets and programs for each manuscript and presentation and for the studies as a whole at the end of each trial. | | | | | P | | |

| TASK | DESCRIPTION | *RESPONSIBILITY* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **NHLBI OVERSIGHT** | **STEERING CMTE** | **CLINICAL CORE** | **STAT/DATA CORE** | **CLINIC SITE** | **DSMB** |
| | Archive CCC clinical data sets and programs for each manuscript and presentation and for the studies as a whole at the end of each trial. | | | | P | P | | |
| | Archive all study documents that are source documents | | | | P | P | P | |

**TABLE KEY**
**P =** Primary responsibility for the completion of the task
**O =** Oversight responsibilities, including final approval of materials/decisions stemming from the unit with primary responsibility
**R =** Review and approval of materials

## 4) Site Start-Up Requirements

1. Conflict of Interest-let CCC know if you reported this on your IRB application
2. Copy of IRB letter of approval
3. Copy of consent stamped with IRB approval
4. Verify your staff completed bleeding assessment training through the recorded webinar
5. Verify your staff completed visual assessment training through viewing the training video on the website
6. Verify your staff completed database/forms training through the recorded training video on the website
7. Verify your staff completed Protection of Human Subjects training
8. Verify your staff completed local HIPAA training, other IRB mandated local site training

## 5) Recruitment

Each PI will make presentations to the staff at their local cancer treatment center to educate them on the potential benefits and risks to study participation. The attending physicians and heme-onc fellows will be consulted by the PIs and RCs to identify potential subjects, and to answer questions about potential subjects. Attending daily hospital rounds is another way to recruit subjects. Generally, the daily intake roster is reviewed by the Research Coordinator to identify potential subjects. See protocol for further details and inclusion/exclusion criteria. You must have the permission of the patient's attending physician or treatment team to approach them for the study. See Protocol Section 5.

## 6) Screening & Eligibility Criteria Work Flow

Each Principal Investigator will train their staff on how to identify potential subjects using their medical records system at their site's cancer treatment center and affiliated hospital(s). This may include a daily intake log. The Research Coordinator at each site is responsible for obtaining a partial waiver of consent and HIPAA requirement from their IRB for the purpose of screening and identifying potential subjects. The protocol outlines inclusion/exclusion requirements on Protocol Section 4. With the local IRB's permission, potential subjects' medical records are examined for patients who meet inclusion and exclusion criteria. Some potential subjects can be eliminated immediately by criteria that will not change, such as a history of thromboembolism. Some potential subjects will have to be watched until it gets closer to the time of treatment or transplant when they can be approached for enrollment if they still qualify. See Protocol Sections 4-5. If the number of eligible screened subjects exceeds the number that can be enrolled at any given time, coordinators will preferentially attempt enrollment of underrepresented race and ethnic groups.

If the site has an electronic system to document screening and/or watching potential subjects, it may be used. Sites may also use a paper system to screen/watch potential patients. Regardless of site specific documentation, all sites must document screened subjects in the database. It should include name, medical record number, and case ID. It can include additional notes such as date of chemotherapy, date of transplant, etc. If the potential participant later refuses, screening information containing protected health information is destroyed. All reasons for exclusion for each screened subject are recorded on the screening form in the electronic database.

### 6.1 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) *(this may also include subjects who are unable to comply with treatment and monitoring due to planned follow-up at an outside facility/outside of the region, or*

*potential subjects who do not speak and/or read the English language and do not have a translator available for study activities)*

**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

## 7) Informed Consent and HIPAA process

The FDA, DSMB, and IRBs at each site will approve the protocol and informed consent (IC). The IC will be as consistent as possible between the sites, taking into account regional differences in IC layout. Each site is responsible for submitting annual reports and paperwork necessary to keep the IC approved and up to date. The DCC will ensure that each site's IC has not expired and is active. Each site's Research Coordinator will ensure that the HIPAA form is up to date and compliant with local requirements.

Potential subjects who meet eligibility requirements and have permission from their primary attending physician may be asked by a trained member of the study team if they are interested in participating in a research study. If they are interested, they will be given the IC to look over with the help of study personnel. Questions will be answered and potential subjects will not be rushed through this process. If they agree and can return demonstrate understanding of the study, the IC will be signed along with the research HIPAA form. The IC and HIPAA forms are copied and given to the subject, while the originals are retained in a secure study file. Sites must maintain signed IC forms for at least three years after study

completion or termination. The database MOO gives further directions for entering screening, consenting, randomizing, and activating subjects.

Potential subjects are allowed to think about it and have the RC/RN return later for follow up. If the potential subject is too tired to participate in a discussion of the study, the IC and or trifold brochure may be left with them, and the RC returns later for follow up. If the potential subject refuses, (s)he is thanked, and their consent status is updated on the screening form. If the potential subject cannot answer on his/her own, the RC may refer to their legally authorized representative (LAR) or family member in charge of their care to aid in the consent process.

## 8) Study Intervention

### 8.1 Enrollment

The subject will sign consent(s). Provide the subject a copy of the consent form(s). Complete the enrollment form on the database. Study personnel should take precautions to ensure that only subjects who meet inclusion/exclusion criteria are enrolled. A double check of all requirements in the protocol, or having a colleague verify that all requirements are met is a good policy.

If a subject is on their menstrual cycle and it is unable to be determined whether a grade 2 bleed is present, the subject should not be enrolled until menstrual bleeding is resolved.

### 8.2 Pre-Randomization

This is the time between the initial screening/enrollment and the date the subject is randomized to receive tranexamic acid or placebo. The subject will not receive study drug during this time. Platelet counts should be closely monitored during this time period in anticipation of randomization. Data collection should occur per Protocol Section 8.1-8.2. Study personnel should verify the subject's eligibility on a daily basis via medical record review. Several possible scenarios in which a subject could become ineligible during this time period are described below. Subjects may become ineligible for reasons other than listed here. If the subject becomes ineligible, complete the end of study database form.

**8.2.1** If the subject becomes ineligible due to grade 2 or higher bleeding: do not randomize. The subject is eligible for randomization later if the bleeding resolves and the platelet transfusion threshold remains <10,000, and the subject has not lost eligibility for any other reason. Do not fill out an end of study form until the study staff has determined it is unlikely that the subject will become eligible for randomization at any time.

**8.2.2.** In some cases of grade 2+ bleeding, the clinical team may raise the platelet transfusion threshold. In this event, do not randomize. The subject is eligible for randomization later if the transfusion threshold is lowered back to <10,000, and the subject has not lost eligibility for any other reason. If the subject remains ineligible complete the end of study form.

**8.2.3.** If a diagnosis of DIC is made by the clinical team prior to randomization, do not randomize. An end of study form should be completed. If the DIC resolves and the subject has not lost eligibility for any other reason, they will become eligible for randomization. In this scenario you may re-screen the same subject under a new case, using the same site linking ID as previous. Follow your local IRB policies to determine if the subject needs to be re-consented.

**8.2.4** If a subject is on their menstrual cycle and it cannot be determined if there is grade 2 bleeding, the patient cannot be enrolled, randomized or activated until this is resolved.

*Informed consents and other study files for subjects who are permanently removed from the study prior to randomization should be maintained per institutional standards. See section 7.

### 8.3 Randomization

When the platelet count is expected to fall below 50,000, a member of the study team arranges for a urinalysis to be performed and a DIC panel to be drawn. The DIC panel includes Prothrombin Time, Partial Thromboplastin Time, D-Dimer, and Fibrinogen. The urinalysis may be performed up to 72 hours prior to randomization and the DIC panel may be performed within 24 hours before or after randomization with results reviewed before activation. The subject should be assessed by study personnel prior to

randomization in the database, in order to ensure the subject remains eligible for randomization. After assessment, study personnel will complete the randomization form in the database. Upon completion of the form, an e-mail will be generated to the staff member's e-mail. Study staff should forward this email to their IDS pharmacy and include the subject's name, medical record number, and date of birth. Protected health information should not be sent to the DCC or the CCC.

The data entry system has the ability to randomize subjects quickly without entering all required laboratory data. While you will need to verify meeting eligibility, you will not have to enter dates, times, and exact counts before randomization.

If outpatient, the subject should begin the outpatient bleeding diary. If inpatient, study personnel should begin daily visits per protocol section 8.3.

## 8.4 Randomization to Activation

Subjects will be followed per protocol section 8.4. Complete data collection and daily forms on the database per protocol section 8.4.

## 8.5 Activation

When the platelet count drops below 30,000, the subject is "activated" and the subject should begin study drug. There may be a delay between activation and the first dose of study medication due to site-specific logistical constraints. If grade 2 bleeding or greater occurs at this time point or in the 48 hours prior, do not begin study drug. The subject may be eligible to start study drug later if/when the bleeding resolves. At activation, study personnel will notify the IDS pharmacy that the subject is ready to begin study drug. Study drug treatment may be initiated in IV or PO routes at the discretion of the subject, study personnel, and/or clinical team. Complete data collection and daily forms on the database per protocol section 8.5. Continue to follow subjects per protocol study schedule.

Any patients unable to tolerate or absorb oral medication (per the discretion of the investigator or physician) will receive TXA or placebo in IV form. Subjects may not receive IV study drug in the outpatient setting. Subjects may be switched at any time from oral to intravenous routes or vice versa, depending on their medical condition during the treatment period.

## 8.6 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.
- Or Oral Administration: tranexamic acid 1.3 g every 8 hours or an identical, inert placebo capsule

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

| ***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* |

## 8.7 Treatment Period

Inpatient subjects are assessed daily by a trained member of the study team and outpatients are assessed at least once a week when they come to the outpatient clinic for regularly scheduled

appointments. Outpatient subjects are asked to fill out a daily bleeding diary, which is reviewed with the coordinator at the weekly visit. Thrombotic assessment is performed by chart review daily. Inpatients and outpatients are given an ocular assessment once a week by a trained member of the study team. Laboratory assessments (hematocrit, hemoglobin, platelet, coagulation profile, serum creatinine, total bilirubin, white blood cell, total neutrophil count) are collected as per standard of care and documented on the daily forms on the database. Data on granulocyte, platelet and red blood cell transfusions and adverse events are collected and documented on the daily form on the database.

### 8.8 Stopping of Study Drug

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

- It has been 30 days since the subject was first activated to the randomized study drug.
- 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.
- 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.
- The subject receives open label TXA, or other anti-fibrinolytic agent or pro-coagulant drug, (e.g., EACA, DDAVP, recombinant Factor VIIa, or Prothrombin Complex Concentrates). Use of these agents will be recorded in study data.
- The subject begins anticoagulant or antiplatelet therapy.
- The subject has visible hematuria.
- The subject has a diagnosis of thrombosis.
- The subject develops sinusoidal obstructive syndrome (SOS), also called Veno-Occlusive Disease (VOD).
- A recurrent incident of central line occlusion.*
- 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.

*The definition of a central line occlusion will be considered when all lumens are occluded, resulting in the inability to access or infuse through the central line without instillation of a fibrinolytic agent and/or removal of the line. It will not require radiographic or ultrasonographic evidence for diagnosis. If the line becomes functional after simply re-positioning the patient or “de-tangling” the lumen(s), the criteria for a line occlusion will *not* be considered met. A recurrent incident is when this definition is met on two separate occasions while the subject is receiving study drug. It is acceptable to have a resolved line occlusion at any point prior to activation and this occlusion will not be counted towards the two occlusions allowed while on study drug.

### 8.9 Holding and Re-starting of Study Drug

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

- A diagnosis of DIC is made by the clinical team.
- Central line occlusion occurs (drug must be permanently discontinued if central line occlusion recurs).

Study drug may be held at the discretion of the subject or the clinical team for any reason. The reason for holding should be documented on the daily form in the database and coordinators should mark the appropriate box on the daily form until the drug is restarted or any other stopping criteria are met. The

maximum amount of time allowed on study drug is calculated as 30 days from the day of activation, not the total number of days on study drug.

### 8.10 Participant Evaluations and Follow-up

See study protocol Section 8 and database MOO for details of data entry and follow up visits for the study.

The outpatient diary and/or inpatient RN/RC assessments are required for at least 30 days after drug activation or randomization if drug is never activated. After the subject stops the drug, you must continue with once weekly eye exam and daily diaries/assessments for 14 days or for 30 days post activation, whichever is greater. You then collect the diaries between 14-21 days after the drug is stopped and call the subject on day 30 (-1/+6) after stopping drug. A final call is made on day 120 (+3) after activation. If the subject never activates, their chart will be reviewed for 30 days after randomization and an end of study form will be completed at that point. The 30 and 120 day follow-up forms are not required in this case.

Total serum bilirubin will be collected, when available, for all days of the safety period (up to 6 weeks but at least 30 days). The baseline total serum bilirubin shall be within 7 days of day 1 of activation. Bilirubin will be collected at least weekly while on active drug.

In the event that the study team is unable to reach a subject for follow-up, a public record search should be performed to aid in determining if the subject is alive at the follow-up time points. Any identification of death (by an obituary, any other public record, or the medical record) must be reported to the DCC within 24 hours by e-mail (see protocol section 16.3.4.).

## 9) Remote Monitoring of Study Subjects

Although the study team will not actively enroll subjects who plan on receiving follow-up care at a non-study site, in some situations, a study participant may decide to receive follow-up care in a distant town or state. In this situation, the determination as to whether or not the subject should be discharged on study drug is at the discretion of the site PI. The research coordinators will promptly inform the site PI, DCC and local IRBs via email or site specific channels if this scenario occurs. Study personnel should plan to perform study activities as best as possible, understanding that some study activities, such as the bleeding and ocular assessments, will need to be modified. Research coordinators may use the following checklist to ensure that the protocol is followed as closely as possible.

***Guidance Checklist for Remote Monitoring of A-TREAT Subjects***

1. Obtain the local provider (name, phone), clinic (name, phone), and hospital(s) name and town

2. Obtain a signed release of medical records for research for each local clinic and local hospital(s)

3. If the subject is currently on active study treatment, ask the PI to determine if the subject may discharge with the study medication

4. Provide enough outpatient diaries for the subject to complete through the end of active treatment and the safety period

5. Provide enough stamped return envelopes for diaries to be returned to RC weekly, or pool if close to end of collection period

6. If the subject is to be discharged with study medication, provide a box and return shipping label addressed to the site's IDS pharmacy. The shipping label must have a tracking number.

7. Communicate with the subject and his/her caregiver:

a. How to fill out the bleeding diary and return it in the mail

b. What to do if your vision changes

c. Why it is important to go to clinic for your blood draws and follow ups

d. What to do if you have questions or concerns

8. Give subject and caregiver business cards for the PI and the RN/RC

9. Set up a time to call the subject for a phone assessment

## 10) Data Collection and Study Forms

A RN/RC worksheet has been prepared to aid in obtaining study related subject information. All study sites must use the CCC approved current version of the ATREAT RN/RC Bleeding Assessment Worksheet. Complete this worksheet by hand, then use the data collected in this worksheet to complete the web-based data entry forms. Data collection should be appropriately prioritized for safety reporting as described below in Section 13. In general, there is a 72 hour window for completing data entry in the database for all non-safety related information, in order to allow for weekends and times of high patient loads. Note that there is a potential for a missed or late safety alert generation when data is entered at a later date.

### 10.1 Data Collection Clarifications

- Donor ABO/Rh type should not be entered for double or triple cord transplants. The box should be left blank on the daily form.
- HLA antibodies (PRA) may be entered on the enrollment form, if available. It is optional to enter these data.

See database MOO for additional details on data collection and entry in the web-based system.

## 11) Study Drug

The IDS Pharmacy at each study site receives the oral TXA/Placebo from CoreRx. It will be logged in, dispensed, and tracked per Pharmacy Manual of Operations and local practices at their site. The CCC communicates with the IDS Pharmacy regarding inventory issues. Product may also be transferred from one to another, per IDS Pharmacy Manual of Operations. Only UW IDS and UW CCC team members may speak directly with CoreRx. See study protocol Section 6 for details of study drug intervention regarding dose, frequency, route, etc.

Whenever possible, a weekly pill count shall be performed by pharmacists, or non-study professional staff such as Medical Assistants and Registered Nurses, using a standard pill counting tray. The IDS pharmacy distributes the TXA or placebo to study participants. The RN/RC may also sign out medication on behalf of patients to coordinate access to study medication.

Quality Control Procedures: CoreRx shall be responsible for quality control and testing of the product prior to release. The CCC PI shall approve and review CoreRx quality control reports.

## 12) Blinding and Unblinding

The IDS Pharmacy and a few members of the DCC (determined by the DCC PI) are to remain un-blinded throughout the study. All other personnel are to remain blinded. The RN/RC shall evaluate the subject in person prior to reading their clinic notes in the medical record that morning. The clinical care team shall consult with the PI or his/her designee in cases where emergency un-blinding is requested. Should it be determined that un-blinding is clinically indicated, the IDS Pharmacist shall be contacted for this information. See IDS Pharmacy MOO and protocol Section 7.1.3 as well.

## 13) Concomitant Medications

The RN/RC should review subject medications with the site PI or his/her designee at enrollment, and report any new or additional medications ordered which relate to bleeding or thrombosis. Participation in

the study will be discontinued if a subject is prescribed other anti-fibrinolytic medications or pro-coagulant agents (e.g. DDAVP, recombinant Factor VIIa or Prothrombin Complex Concentrates (PCC). See stopping rules in protocol section 6.3.

## 14) Safety Reporting

The RN/RC shall consult with the site PI or his/her designee with questions or concerns about a subject's medical condition and any changes in it. The site PI or his/her designee shall determine if the event, change, or symptom is an AE, SAE, or SUSAR which is reportable to the DCC, DSMB, FDA, and/or IRB. See Figure 5 of protocol. All serious adverse events, including death, must be reported to the DCC by e-mail within 24 hours of discovery. The Serious/Unexpected Adverse Event form must be sent to the DCC by the end of the month. 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. The SAE form must be completed by the Investigator 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 database to the DCC as soon as possible. The initial report shall be followed by detailed, written reports as requested by the DCC. 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).

Reference the Data Forms MOO for further instructions for completing alert forms on the database. See protocol sections 9, 11, 15 and 16 for additional information on safety reporting.

Medwatch: The FDA Safety Information and Adverse Event Reporting Program
http://www.fda.gov/Safety/MedWatch/default.htm

## 15) Study Assessments

**a. Ocular Assessment:** Ocular Assessment training must be done prior to subject assessment. See web for training materials. See Protocol section 11.2. 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 activation up to and including the day of active treatment, then weekly* until two weeks post discontinuation of study drug. Report any visual changes identified using an alert form on the database. Visual/ocular changes should also be reported to your site PI.

*Weekly is defined as once during a period starting on a Monday and ending on a Sunday.

**b. Thrombotic Assessment:** During the active study period, assessment for signs/symptoms of thrombosis should be performed on a daily basis via patient examination, interview, and/or medical chart review. Suggested questions to the patient: "Do you have any redness or swelling in your arms or legs"? "Do you have any pain in your arms, legs, or chest?" Radiology/ultrasound records should be reviewed daily to rule out thrombosis. If thrombosis occurs, the study medication should be stopped per stopping rule 6.3.7, the PI notified, and an alert should be sent on the database. Thrombotic assessment is also performed via chart review and patient interview at the 30 and 120 day follow-up time points.

**c) Bleeding Assessment:** RN/RC training for performing the hemostatic and bleeding assessment must be complete prior to subject assessment. The Bleeding Assessment is designed to capture any and all signs of bleeding every day a subject is in the ATREAT Trial. The RN/RC performing the Hemostatic Assessment generally includes a physical assessment, interview of the patient, and medical chart review. The physical assessment and interview must be completed prior to the medical chart review to eliminate bias. While observations and inquiries of the patient will be performed throughout the day by clinical staff, at least one continuous head-to-toe assessment of the patient is required by research staff as well. For inpatients, a qualified, trained medical professional will assess and interview the subject on a daily basis, at approximately the same time each day. For outpatients, a qualified, trained medical professional will assess and interview the subject at least once weekly. In both inpatient and outpatient settings, ensure that the most private area possible is secured for patient interviews and assessment.

The findings from the assessment are recorded on the paper hemostatic assessment form and the daily form on the database. All study sites must use the CCC approved current version of the ATREAT RN/RC Bleeding Assessment Worksheet. Outpatient subjects fill out a bleeding diary form each day. If there is missing information on the outpatient diary, study personnel should not attempt to fill in the information for the subject, since the outpatient diary is the subject's source documentation. If study personnel wishes to add clarifications or additional information to the outpatient diary, a separate piece of paper with the necessary information may be stapled to the subject's outpatient diary. If an outpatient diary is missing information, a note to file should be created for the subject's file which documents that the outpatient diary is incomplete and the reason why. Trained study personnel will review the diary entries with them at least weekly. See figure 2 and protocol section 11 for the schedule of assessments and further details.

COMPONENTS OF THE HEMOSTATIC ASSESSMENT

Physical Assessment and Patient Interview

The purpose of the physical assessment and interview is to seek out firsthand evidence of bleeding, either from your direct observations of the subject (and their bodily fluids), and/or a direct report from the patient, family members and nurse caring for the patient. The patient has the right to refuse any portion or all of the physical assessment and interview. If this occurs, note this on the bleeding assessment form. If unable to complete part or all of the physical assessment or interview, mark the appropriate question as "N/A" (Not asked, Not applicable or Not assessed).

Medical Record Review

The goal of the medical record review is to note any documented occurrence of bleeding. The case report form has been designed to collect all observations and symptoms related to bleeding as recorded by the WHO Grading system.

Per standards of care, hospital patients are assessed on a continual basis throughout the day. Findings and treatment plan(s) can be determined through a review of the medical record. Findings described in one area will suggest a path to follow where you may find corresponding, and possibly more detailed, information. For example, physician orders will give you a clear idea if the patient is receiving the expected treatment for their condition, or if there was an emergency, and what action was ordered. Be alert for written orders requesting that a consulting specialist examine the patient. What are the signs and symptoms precipitating such a request? Ideally, a narrative of events giving the rationale, and expected response, can be found in the progress notes. Many hospitals have integrated progress notes. If your institution has specialty progress notes in different areas of the chart, look through all of them. Review all flow charts to get a feel for the patient's usual vital signs, and daily routine. Once you have observed the normal parameters for this patient, you will be cognizant of any changes, enabling you to provide accurate data relating to patient bleeding.

Supplemental fluids, including blood products, will be listed and included in the daily Intake and Output flow sheet, and possibly elsewhere. All procedures will have an accompanying note in the chart. Many invasive procedures will be followed with a full report. The laboratory section of the chart will reveal results from all specimens taken from the patient. A final report may take several days for certain specimens.

Oral and Nasal Evaluation

A. Physical Assessment: Inspect both the oral and nasal mucosa with a light source. Is there any sign of active bleeding? Any blood filled bullae in the mouth? Are petechiae of the oral mucosa present? Do you see any evidence of dried blood in the nares?

B. Patient Interview - Suggested questions for the patient:
Have you had any bleeding from your mouth since the previous assessment?
If so, how long did it last? Did it happen again?

Have you had any nosebleeds since the previous assessment? If so, how long did it last? Did it happen again?

C. Medical Record Review: Is there a reference in the progress notes of oropharyngeal bleeding or epistaxis? If so, how many episodes? What was the total duration of any bleeding since last assessment? Did any bleeding occur that required intubation?

Skin, Soft Tissue and Musculoskeletal Evaluation

A. Physical Assessment: *(Note: Keep patient warm and covered at all times. As the assessment proceeds expose only the areas of the body that are necessary in order to maintain patient comfort. It may be easier to conduct this assessment with the subject in bed.)*

*As you assess the patient's face, neck, torso, and all extremities, be alert for appearance of any new (since the previous assessment) hematoma(s), bruising, petechiae, or purpura. Measure and note the size and type findings. While examining the skin, observe any intravenous or puncture sites to see if there is blood oozing around the insertion site.*

*We are looking for spontaneous bruising. It may be difficult to grade bruising when there is bruising within a rash. Consult your PI to assist with grading in these situations. If your local IRB permits, you may take a picture of the site, and send to your PI. The picture may not be retained after your PI reviews it.*

B. Patient Interview - Suggested questions for the patient:
Have you noticed any new bruises or "blood spots"?
Do you know when they appeared?
Do you have redness or swelling in your legs or arms?

C. Medical Record Review: Do the Progress Notes reflect the appearance of hematoma, bruising, petechiae or purpura? Have any of the health care providers noted a hematoma in soft tissue or muscle? Are there any complaints of joint pain noted? Is there a procedure note describing a joint aspiration? If so, what is the description of the removed fluid? What is the lab analysis of the removed fluid? Are any signs/symptoms of DVT present in the medical record, such as redness or swelling in the arms or legs? *Note: It is possible that these results will take a few days to come back. Remember to return to the chart and obtain the results prior to completing the case report form.*

Gastrointestinal/Genitourinary/Gynecologic Evaluation

A. Physical Assessment: If the patient has a nasogastric tube, note the color of the drainage, if any. Is it pink, red or dark (sometimes referred to as coffee grounds)?
If the patient has a urinary catheter, check the color of the drainage for blood.
If there is urine or stool in the patient's room, note the color and appearance.

B. Patient Interview - Suggested questions for the patient:
Have you vomited any blood during this assessment period?
Have you had any tarry stools during this assessment period?
Have you had any bright red stool during this assessment period?
Have you seen any blood in your urine?
If the patient is female, ask if she has had any abnormal or unexpected vaginal bleeding? If so, was this bleeding in addition to her normal cycle, or heavier than normal in usual cycle? If this patient is taking prescribed hormone therapy, is this an episode of breakthrough bleeding?

C. Medical Record Review: Review progress notes, flow charts, imaging reports, operative and procedure notes for a record of any diagnostic procedures or therapeutic interventions, specifically related to a bleeding or suspected bleeding event. Check X-Rays, CT scans, MRI images, stool studies and urinalysis/urine dipstick results. Has the patient undergone an endoscopy, laparoscopy, or paracentesis? If there is an indication of bleeding, or intervention

due to bleeding, did the patient experience any hemodynamic instability (i.e., drop in BP, increase in heart rate)?

Pulmonary Evaluation

A. Physical Assessment: If the patient is artificially ventilated, and you are there when they are being suctioned, look for evidence of blood or blood-tinged secretions. Unless the patient has an episode of hemoptysis while you are with him/her, the pulmonary assessment for bleeding will be most effective with questions asked directly of the patient and through the medical record review.

B. Patient Interview - Suggested questions for the patient:
Have you coughed up blood? If so, was it bright red, dark, or blood tinged?

*C.* Medical Record Review: Is there a record of hemoptysis in the progress notes? Check for procedure notes or a report of a bronchopulmonary lavage. If so, what are the findings, what did lab analysis of lavage specimen reveal? *Note: It is possible that these results will take a few days to come back. Remember to return to the chart and obtain the results prior to completing the case report form.*

Body Cavity Evaluation

A. Physical Assessment: It is unlikely that you will be able to determine if there is any blood in the patient's body cavities by assessment alone. Information to determine if there is any blood in a body cavity is likely to be self-reported by the patient or come from the medical record.

B. Patient Interview - Suggested questions for the patient:
Have you had a procedure to remove fluid from the abdomen or chest?

C. Medical Record Review: Check for a record of paracentesis or thoracentesis. What was the description of the aspirate? Was aspiration effective? If not, did the patient need additional intervention? Did the patient experience any change in vital signs consistent with a bleed?

Eye Bleeding Evaluation:

A. Physical Assessment: Look at the patient's eyes. Have the patient aim their eyes upward, downward, and to each side. Is there visible bleeding in the white part of either eye?

B. Patient Interview- Suggested question for the patient: Have you noticed that the white part of your eye has turned red colored-not just irritated?

C. Medical Record Review: Check for a record of retinal bleeding, vitreous bleeding, or subconjunctival hemorrhage. Check for a record of visual impairment with any eye bleeding.

Neurological Evaluation

A. Physical Assessment: Neurological status in relation to any bleeding is difficult to obtain with a general assessment. However, observation of a patient's general mental status, level of consciousness, coordination, voluntary and involuntary movements may provide some cues.

B. Patient Interview - Suggested questions for the patient:
Have you had any trouble seeing (other than your usual need for corrective eyewear, if applicable)?
Have you had any changes in hearing? Any ringing in the ears?
Have you noticed weakness on either side?
Have you developed any difficulty walking since the last assessment?

C. Medical Record Review: Are there orders for a neurologic or ophthalmologic consult? If so, what are the findings? Is bleeding the source of any symptoms? Check for any diagnostic imaging and

findings. Did the patient undergo a lumbar puncture or imaging study? Again, what are the findings? Is it related to bleeding? If any specimens were obtained, record findings if appropriate.

Invasive Sites Evaluation

A. Physical Assessment: Is there any blood oozing around the insertion or exit site?

B. Patient Interview: Suggested question for the patient:
Have you noticed any bleeding or oozing around your IV catheter or drain site? If so, how long did the bleeding/oozing last?

C. Medical Record Review: Check for a record of any blood oozing around the insertion sites of any catheter, drain, or puncture sites.

Hemodynamic Instability

Hemodynamic instability may include a decrease in blood pressure frequently accompanied with increase in heart rate. While there is no plan to record specific vital signs, one of the effects of a severe bleeding episode is compromise in hemodynamic status. The medical record will provide additional information as to the causative factors describing other systemic changes associated with shock. Some of the known treatments and interventions associated with acute shock include administration of fluids, emergent transfusions, initiating vasopressors, and transfer to an intensive care unit or to the operating room. Check with the site PI to see if this may be considered an AE/SAE/SUSAR.

## 16) Data and Safety Monitoring Activities

See study protocol Sections 18 for Data Safety and Monitoring Board information.

Research Coordinator and Study Personnel should pay particular attention to the following:

1) The need for daily review of each patient's renal status while on study drug, so that the PI or designee can be notified and orders written for changes in drug dosing per Protocol Section 6.5.

2) The need for daily review of each patient's thrombotic events while on study drug, in order that the PI or designee can be notified and they can permanently or temporarily stop the study drug, and the events reported to the DCC in an expedited fashion.

3) The need for daily review of hematuria while on study drug. The drug should be held and the PI or designee notified so the drug can be permanently stopped if appropriate.

4) The need for daily review of radiologic studies. This is necessary to rule out symptomatic thrombosis or incidental findings of thrombosis during the study period. Radiologic studies may also provide bleeding information and/or help to identify adverse events.

5) The need to notify the PI or designee as soon as possible for review of all possible SAEs that might be considered SUSARs in order that appropriate expedited reporting of such outcomes can be made to the DCC as appropriate.

6) The need to report all visual changes to the PI or designee, and grade 3 visual changes promptly reported to the DCC.

7) The need to report all deaths promptly to the DCC.

8) The need for daily review of each patient's platelet counts to allow prompt randomization, activation, and/or stopping of study drug.

Data collected for items 1-7 above have priority on busy days or weekends, so that safety is addressed promptly. This allows changes in dosing and DCC alerts. When data is entered into the web-based data entry system, there are some DCC alerts automatically generated. Study personnel should not rely on just these alerts, but be aware of critical safety reporting in the study.

## 17) Study Compliance

The site PI is responsible for study compliance. The DCC will monitor study compliance. In the event of an FDA audit, the investigator must allow FDA access to the study records for inspection and copying. See protocol Section 15.

## 18) Data Management

The DCC and DSMB statisticians are responsible for overall data management. Site PIs are responsible for collection of data at their sites. See protocol sections 14 and 15 for further details.

## 19) Study Completion

**19.1 Subject completion**: Subjects will exit the study after the day 120 post activation of study drug time point requirements are fulfilled.

**19.2 Withdrawal**: Subjects are free to withdraw their consent from further participation in the trial at any time. If this occurs, ask the subject to grant consent for the study team to complete follow up calls and/or passively monitor their electronic health record. If the subject wishes to withdraw consent for all study procedures including study visits, follow up calls and monitoring of electronic health records, complete an End of Study form and document the reason for withdrawal, Explain to the subject that any data obtained up until the point of consent withdrawal will be included in study analysis.

**19.3 Death**: Notify the PI and complete an end of study form. Death of a subject must be reported to the DCC within 24 hours of discovery by e-mail. In the event that the study team is unable to reach a subject for follow-up, a public record search should be performed to aid in determining if the subject is alive at the follow-up time points. Any identification of death (by an obituary, any other public record, or the medical record) must be reported to the DCC within 24 hours of discovery by e-mail (see Clinical MOO section 8.9 and protocol section 16.3.4.).

## 20) Study Close-Out

Following completion of enrollment, the CCC will provide a memo to sites noting that enrollment is completed and with further instructions on close-out procedures. Unused or expired study drug should be disposed of on-site, according to local standard operating procedures. See Pharmacy MOO section 11.1 for further details. Sites must maintain signed Informed Consents, CRFs, study documentation, and source documents for at least three years after study completion or termination. Local institutional policies, IRB policies, and NHLBI policies should be followed when closing out a study. See Section 16.2 of the protocol. The DCC is responsible for notifying local sites if there is missing data or if further information is needed.