

AWARD NUMBER: W81XWH-13-2-0090

TITLE: Prehospital Tranexamic Acid Use for Traumatic Brain Injury

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES					
14. ABSTRACT The primary aim is to determine the efficacy (comparing 6 month GOSE) of two dosing regimens of TXA initiated in the pre-hospital setting in patients with moderate to severe TBI (GCS score 3-12).The first year has been spent in preparation for study implementation including approvals by the ROC Protocol Review Committee and Data, Safety Monitoring Board, as well as obtaining an FDA IND and Health Canada CTA. The documents for the first site approval were sent to HRPO on June 19, 2014 and final approval by the Sec. Army occurred on 2/8/2015. A web data entry system to collect the patient data and check for errors (and a detailed Manual of Operations) was completed. Enrollment started on 5/18/2015. Nine of 12 sites have started enrollment. One Canadian site had to suspend enrollment due to issues of patient privacy. It is expected that all sites will be enrolling by January of 2016. Enrollment is projected to be completed by November of 2016 with the last GOSE evaluation in early 2017.					
15. SUBJECT TERMS Traumatic Brain Injury (TBI), TXA, prehospital					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 100	19a. NAME OF RESPONSIBLE PERSON USAMRMC
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1. Introduction

The primary aim of this exception from informed consent study is to determine the efficacy of two dosing regimens of TXA compared to placebo initiated in the prehospital setting in patients with moderate to severe TBI (GCS score ≤ 12) using the 6 month GOSE. The secondary aims are to compare TXA to placebo in clinical outcomes (ICH progression, Marshall and Rotterdam CT classification scores, DRS at discharge and 6 months, GOSE at discharge, 28 day survival, frequency of neurosurgical interventions and ventilator-free, ICU-free, and hospital-free days), safety outcomes (seizures, cerebral ischemic events, myocardial infarctions, deep venous thrombosis and pulmonary thromboembolism) and mechanistic outcomes (alterations in fibrinolysis based on fibrinolytic pathway mediators and degree of clot lysis based on TEG).

2. Body

Scope of Work

a. Specific Aim 1-to determine clinical efficacy of TXA in TBI as measure by multiple clinical endpoints

i. Major Subtask 1.a.: Obtain regulatory approval by PRC, FDA, DSMB, UW IRB, Health Canada, HRPO/Dod/ACURO

This subtask has been completed with final regulatory approval by the Sec Army on 2/8/2015.

ii. Major Subtask 1.b.: Clinical Site submission to and approval from IRB including community consultation/notification.

There are 12 sites involving 19 receiving hospitals. Below is a table noting the start-up status of each site.

Site	IRB submitted	Final Approval after Community Consultation (CC) & Notification	HRPO Approval Status	Date enrollment started
UW DCC	3/17/2014	4/9/2014	N/A not enrolling site	N/A
Toronto- 2 hospitals	2/2014	3/2014	6/25/2015	8/5/2015
Alabama- 1 hospital	5/8/2014	1/29/2015	5/15/2015	7/24/2015
British Columbia- 2 hospitals	6/5/2014	10/13/2014	6/19/2015	7/16/2015 Suspended enrollment 7/24/2015 due to privacy issues
Cincinnati, OH	5/9/2014	5/15/2015	10/15/2015	?Dec. 2015

1 hospital				
Dallas/Ft. Worth 7 hospitals	4/16/2014	6/19/2014	9/10/2014 8/28/2015	1 hospital started 9/21/2015
Houston, TX 1 hospital	7/9/2014	3/3/2015	5/7/2015	6/24/2015
Milwaukee, WI 1 hospital	5/14/2014	5/11/2015	7/1/2015	8/19/2015
Mayo Clinic, MN 1 hospital	3/17/2015	CC underway	Not yet sent	?Jan. 2016
Portland, OR 1 hospital	5/7/2014	12/19/2014	5/1/2015	5/26/3015
Seattle/King Co, WA 1 hospital	5/23/2014	11/25/2014	4/7/2015	5/13/2015
St. Paul, MN 1 hospital	5/15/2014	9/14/2014	5/28/2015	5/30/2015
Hennepin Co, MN 1 hospital	1/25/2015	9/21/2015	Not yet sent	? Dec. 2015

iii. Major Subtask 2.a.: Study implementation

a. Designing data collection forms

Case forms have been designed with input from investigators and clinical sites. As data entry continues the forms are modified to correct issues and problems.

b. Web programming of forms, imaging/lab reporting, monitoring

Web programming is completed which included beta testing. Error checks are in place and being optimized as needed.

c. Training EMS/hospital staff

Training materials were finalized for training of both the EMS and the hospital staff last year. As issues are uncovered during enrollment training is updated for both the EMS and the hospital staff.

d. Hire and train research staff on protocol

Main coordinators continue to have biweekly calls to discuss study issues (one with investigators and one with only coordinators). Formal training on the protocol and data collection forms occurred in October, 2014 with a webinar that was recorded for future training. Additionally each site has a detailed start-up checklist completed and approved by the Study Monitoring Committee prior to enrolling patients and calls as needed with DCC clinical and regulatory personnel to ensure completion of milestones. Included on this checklist is special documentation for and approval by HRPO.

The items below have not been completed:

- e. **Enroll 1002 subjects-enrollment began May 13, 2015 and as of Oct 27, 2015, 154 patients were enrolled. See Appendix 1 for enrollment tables.**
- f. **Site audits**
- g. **Cleaning and analyzing data**
- h. **CT scan reviews, ICH measurements-training of tech**
- i. **Statistical analyses**
- j. **Manuscript preparation**

b. Specific Aim 2: Determine the safety of TXA in TBI

i. Major Subtask 1: Appoint Medical Monitor

Dr. Eugene Moore is Medical Monitor for the study and receives safety reports monthly. As well, any potential SAEs considered urgent are sent to him as soon as possible following awareness of the SAE.

ii. Major Subtask 2: Collection and review of safety endpoint

Forms are active to collect SAE data after patient enrollment. A process has been developed to address SAE monitoring and reporting. In addition, a process to unblind a patient is in place.

iii. DSMB meetings every 3-6 months

DSMB has approved the protocol and the monitoring tables reviewed the data at their Oct. 22, 2015 meeting with the recommendation to continue the study. The DSMB asked for safety information on the study in January and April 2016 with an interim review of the first 200 patients in approximately July 2016.

c. Specific Aim 3: Explore the mechanism of TXA

i. Major Subtask 1: Collect TEG at sites

All hospitals except three will be able to collect TEG measurements. Currently 91% of patients have the first TEG completed decreasing to 74% by the 48 hour data collection point.

ii. Major Subtask 2: Conducting assays on blood-OHSU

The OHSU coordinating center has finalized the MOP for blood sample processing and is currently receiving and processing labs.

Dr. Susan Rowell submitted an R01 application to NHLBI in May 2014 to obtain additional funding to examine circulating biomarkers of structural brain injury in the patients enrolled in the TXA trial. Dr. Rowell recently received confirmation that the funding for this substudy was awarded. This funding would also provide for pharmacokinetic analyses. A separate local funding source had been secured for the creation of a genomic and transcriptomic repository.

3. Key Research Accomplishments

The research accomplishments since the last annual report:

- 10/17/2014-Draft CT/MRI data collection complete
- 11/01/2014-Regulatory/Start-up milestone tracking system completed
- 11/14/2014-Completion of calls with each of the 12 sites regarding regulatory/start-up milestones and documentation system
- 11/15/2014-Modifications made to web data entry based on beta testing feedback

12/03/2014-OHSU CT/MRI data collection forms finalized
 12/12/2014-CTC obtains final documentation of TEG supply discount
 12/16/2014-SMC approval of performance benchmarks
 12/17/2014-Coordinator training for data entry forms
 12/22/2014-Final MOP for lab processing
 01/27/2015-Sample blood drawing tubes/kits sent to sites. OHSU to send as sites start.
 Supplies have now been purchased.
 01/27/2015-TEG supplies logistics finalized. ROC CTC to place orders as sites start
 02/06/2015-Unblinding center process finalized.
 02/10/2015-Sec Army approval of first TXA site
 02/18/2015-Forms training of sites completed including GOSE administration training
 03/05/2015-Final procedure for TXA in-hospital kit access
 03/15/2015-OHSU identifies CT tech for analyzing head CTs
 03/15/2015-OHSU finalizes transfer process for CT/MRIs
 03/25/2015-Final MOP for study forms
 03/26/2015-HRPO applications sent for five other sites (since 2/17)
 04/03/2015-Amendment 1.2 approved by DSMB
 04/29/2015-In person training meeting during ROC Steering Committee meeting
 04/24/2015-Draft Safety Monitoring Plan sent to Medical Monitor, investigators
 05/13/2015-First site starts enrolling (Seattle-King Co)
 06/10/2015-First site visit to Portland including enrolling site and clinical lab core
 06/16/2015-Final Safety Monitoring Plan signed off by Medical Monitor
 06/20/2015-Ongoing modification to web errors and forms as needed
 07/29/2015-Amendment 2 approved by DSMB

4. Reportable Outcomes

There are no reportable outcomes yet. The group will prepare a methods paper to be submitted to a journal in the next six months.

5. Conclusions

The ROC clinical sites have begun enrollment in the study. It is projected this study will complete enrollment in Nov. 2016 with follow-up to be conducted into early 2017. The NHBLI has provided ROC with the first no cost extension through 12/31/2016 and verbally assured the investigators that a no cost extension will be approved for 2017 in order to complete the study and analyses.

6. References-N/A

7. Appendices

- a. **Appendix 1 Enrollment Tables**
- b. **Appendix 2 Current protocol dated 7/29/2015 (with summary of Amendments 1.2 and 2)**

Early Tranexamic Acid Use for Traumatic Brain Injury

DMRDP Funding Opportunity Number: W81XWH-12-CCCJPC-TACR



DMRDP

PI: Susanne May, PhD; Schreiber/Rowell, MD Org: University of Washington; OHSU Total Award: 4.054M

Study Aims – in subjects with traumatic brain injury:

To determine if 1gm bolus TXA followed by 1gm infusion over 8 hrs, or a single 2 gm bolus TXA improves the following compared to placebo:

- 1.Global neurologic outcome at 6 months by Glasgow Outcome Scale Score (GOS-E)
- 2.28-day mortality
- 3.Progression of intracranial hemorrhage

To determine the safety of TXA as measured by:

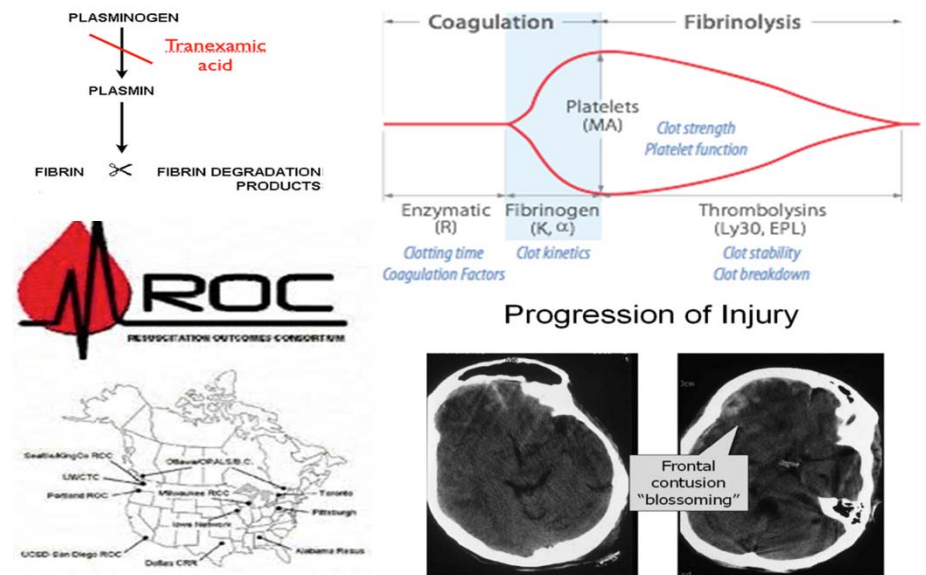
- 1.Thromboembolic events (cerebral ischemic events, MI, DVT, PE)
- 2.Seizures

To explore the mechanism of TXA via:

- 1.Thrombelastography
- 2.Analysis of coagulation pathway mediators

Approach – to be conducted under EFIC

Phase II multi-site randomized placebo controlled trial evaluating the safety and efficacy of 2 dosing regimens of TXA administered within 2 hours of injury to patients with traumatic intracranial hemorrhage.



Timeline and Cost

Activities	CY	13-14	14-15	15-16
Regulatory approval: ROC/FDA/IRB				
EFIC requirements/ Final approval				
Enrollment and follow-up				
Data analysis and submission of primary paper				
Estimated Budget (\$K) Total	\$256	\$2585	\$1214	

Goals/Milestones

CY13 Goal Regulatory approval

- ☒ Submit to ROC PRC
- ☒ Submit to ROC DSMB
- ☒ IND final approval
- ☒ PRC approval
- ☒ Submit to FDA for IND
- ☒ FDA

CY14 Goals EFIC requirements/enrollment begins

- ☒ Sites-DCC submit for IRB approval
- ☒ Submit for Health Canada approval
- ☒ Sites begin community consultation
- ☒ Sites begin public notification
- ☒ Web data entry completed
- ☐ All sites begin enrollment
- ☒ DSMB approval
- ☒ approval

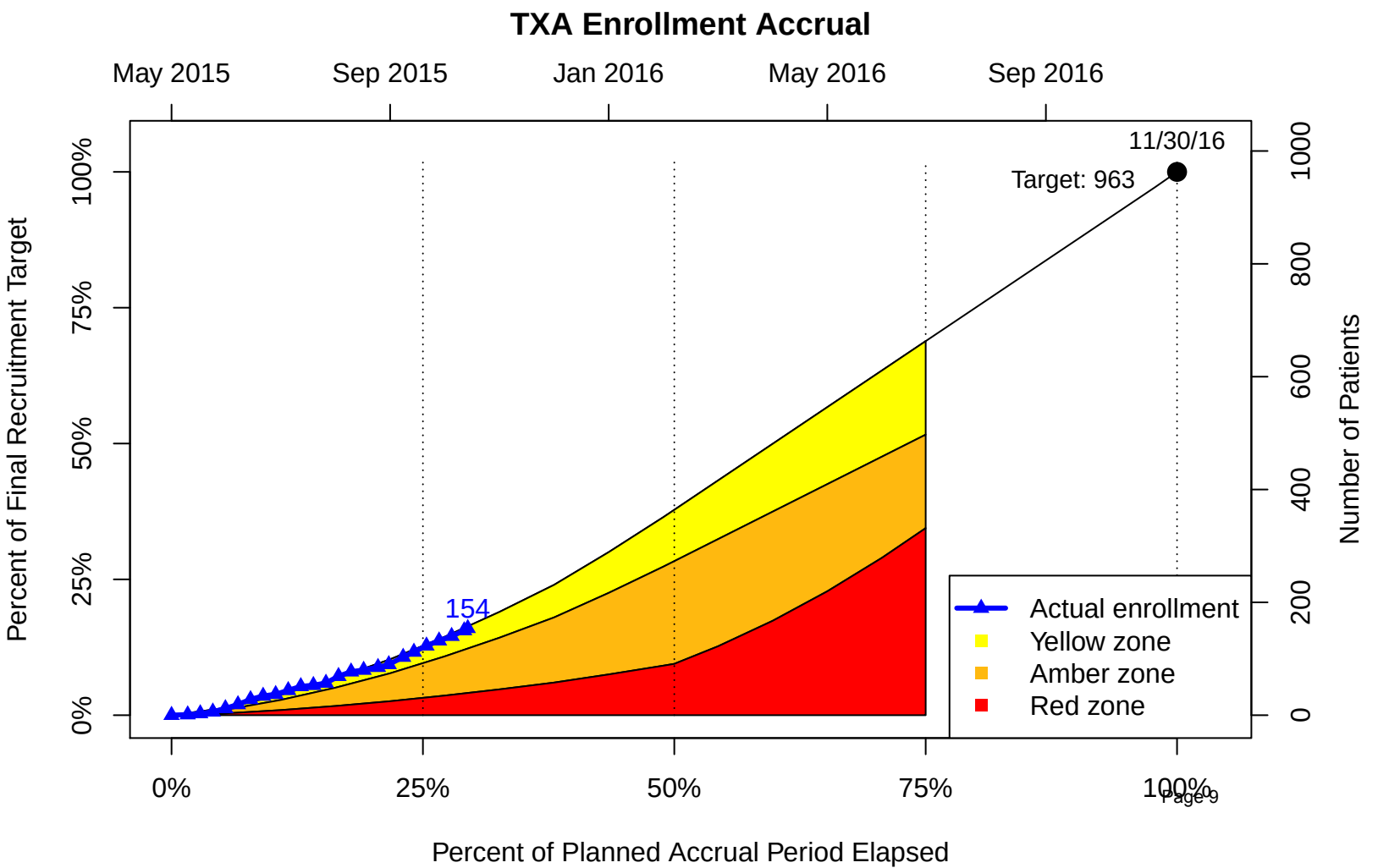
CY15 Goal Completion of enrollment/data analysis begins

- ☐ Complete patient enrollment at all sites
- ☐ Begin data analysis/clean up

CY16 Goal Completion of analysis/primary paper submitted

- ☐ Last follow-up completed
- ☐ Analysis final
- ☐ Primary paper submitted

Updated: Oct 15, 2015, U of W, Seattle, WA



Sites	Last 4 Weeks ¹						Since Beginning of Study					
	Inclusion/exclusion criteria met		Percent of eligibles enrolled	Kit opened but study drug not given (KONG)	Infusion started but inclusion / exclusion criteria not met	Total enrolled ³	Inclusion/exclusion criteria met		Percent of eligibles enrolled	Kit opened but study drug not given (KONG)	Infusion started but inclusion / exclusion criteria not met	Total enrolled ³
	Eligible	Enrolled (Infusion started ²)					Eligible	Enrolled (Infusion started)				
Seattle-King Co.	14	8	57%	1	0	8	81	57	70%	5	1	58
Houston	12	11	92%	1	0	11	32	31	97%	1	2	33
St. Paul (Regions)	1	1	100%	0	1	2	23	18	78%	5	4	22
Portland	5	4	80%	0	0	4	25	14	56%	0	4	18
Toronto	4	2	50%	0	0	2	15	9	60%	0	0	9
Alabama	2	2	100%	0	1	3	8	6	75%	1	1	7
Milwaukee	4	4	100%	0	0	4	7	5	71%	0	0	5
Dallas-Fort Worth	3	2	67%	2	0	2	3	2	67%	2	0	2
British Columbia	0	0	--	0	0	0	0	0	--	0	0	0
Cincinnati	0	0	--	0	0	0	0	0	--	0	0	0
Minneapolis-Hennepin Co.	0	0	--	0	0	0	0	0	--	0	0	0
Rochester (Mayo)	0	0	--	0	0	0	0	0	--	0	0	0
ROC	45	34	76%	4	2	36	194	142	73%	14	12	154

Notes

1. "Last 4 Weeks" includes patients entered into the trial database within 4 weeks of the data extraction date. Thus cases with episode dates more than 4 weeks before the extraction date could be included in these rows.
2. Kit opened but study drug not infused are not included here.
3. Includes all patients for whom the study drug was infused regardless of eligibility status. Does not include kit opened but study drug not infused (KONG).

ROC TXA Enrollment by Agency and Hospital

Data in the database as of: 10/27/2015

(Agency numbers may not add up to site numbers since agency info may not be immediately available)

	Start Date	Eligible	Enrolled eligibles n (%)	Ineligibles enrolled	Total enrolled ¹	Kit opened but study drug not given (KONG)	Hospital Status ³				Sites with Multiple Participating Hospitals											
							Participating	Non- participating	Died in field	Not available yet	BC		Dallas-Fort Worth								Toronto	
											Royal Columbian	Vancouver Gen.	Baylor	Harris	JPS	Methodist-Dallas	Parkland	Plano	Presbyterian			
ROC	05/13/15	194	142 (73)	12	154	14	148	0	0	6	Royal Columbian	Vancouver Gen.	Baylor	Harris	JPS	Methodist-Dallas	Parkland	Plano	Presbyterian			
Alabama	07/24/15	8	6 (75)	1	7	1	5	0	0	2												
Air Methods		0	0 --	0	0	0	0	0	0	0												
Bessemer Fire	07/24/15	0	0 --	0	0	0	0	0	0	0												
Birmingham Fire	09/03/15	6	4 (67)	1	5	1	3	0	0	2												
NorthStar EMS	08/06/15	2	2 (100)	0	2	0	2	0	0	0												
RPS	07/24/15	0	0 --	0	0	0	0	0	0	0												
British Columbia	07/15/15	0	0 --	0	0	0	0	0	0	0	0	0										
Cincinnati		0	0 --	0	0	0	0	0	0	0												
Dallas-Fort Worth	09/21/15	3	2 (67)	0	2	2	2	0	0	0			0	0	0	0	0	2	0			
CareFlite		0	0 --	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
Dallas Fire		0	0 --	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
Irving Fire		0	0 --	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
MedStar		0	0 --	0	0	0	0	0	0	0			0	0	0	0	0	0	0			
Plano Fire	09/21/15	3	2 (67)	0	2	2	2	0	0	0			0	0	0	0	0	2	0			
Houston	06/24/15	32	31 (97)	2	33	1	33	0	0	0												
Milwaukee	08/19/15	7	5 (71)	0	5	0	3	0	0	2												
Flight For Life	09/09/15	1	0 (0)	0	0	0	0	0	0	0												
Franklin	09/18/15	0	0 --	0	0	0	0	0	0	0												
Greenfield	10/05/15	0	0 --	0	0	0	0	0	0	0												
Milwaukee Fire	08/19/15	4	3 (75)	0	3	0	2	0	0	1												
North Shore Fire	10/20/15	0	0 --	0	0	0	0	0	0	0												
Oak Creek	10/09/15	1	1 (100)	0	1	0	0	0	0	1												
South Milwaukee	09/23/15	1	1 (100)	0	1	0	1	0	0	0												
Wauwatosa	09/04/15	0	0 --	0	0	0	0	0	0	0												
West Allis	09/11/15	0	0 --	0	0	0	0	0	0	0												
Minneapolis-Hennepin Co.		0	0 --	0	0	0	0	0	0	0												
Portland	05/26/15	25	14 (56)	4	18	0	18	0	0	0												
Clackamas AMR	05/26/15	7	3 (43)	1	4	0	4	0	0	0												
Multnomah AMR	05/26/15	18	11 (61)	3	14	0	14	0	0	0												
Rochester (Mayo)		0	0 --	0	0	0	0	0	0	0												
Gold Cross		0	0 --	0	0	0	0	0	0	0												
Mayo One		0	0 --	0	0	0	0	0	0	0												
St. Paul (Regions)	05/30/15	23	18 (78)	4	22	5	22	0	0	0												
HealthEast	05/30/15	8	6 (75)	1	7	2	7	0	0	0												
Lakeview	05/30/15	4	3 (75)	1	4	1	4	0	0	0												
St. Croix EMS	05/30/15	0	0 --	0	0	0	0	0	0	0												
St. Paul Fire	05/30/15	11	9 (82)	2	11	2	11	0	0	0												
Seattle-King Co.	05/13/15	81	57 (70)	1	58	5	56	0	0	2												
ALNW	05/13/15	23	17 (74)	1	18	2	18	0	0	0												
Bellevue M1	05/26/15	6	4 (67)	0	4	0	3	0	0	1												
King Co. M1	05/18/15	24	20 (83)	0	20	1	19	0	0	1												
Redmond M1	05/13/15	2	0 (0)	0	0	1	0	0	0	0												
Seattle M1	06/08/15	19	11 (58)	0	11	1	11	0	0	0												
Shoreline M1	05/13/15	7	5 (71)	0	5	0	5	0	0	0												
Toronto	08/05/15	15	9 (60)	0	9	0	9	0	0	0						3	6					
Ontario Air Ambulance	08/05/15	8	6 (75)	0	6	0	6	0	0	0						3	3					
Toronto EMS	08/05/15	7	3 (43)	0	3	0	3	0	0	0						0	0					

Notes

1. Includes all patients for whom study drug was infused regardless of eligibility status. It does not include KONG patients
2. Based on eligibles enrolled, not total enrolled.
3. Counts should add up to "Total Enrolled" column



Susanne May, Ph.D.
Principal Investigator

Graham Nichol, M.D.
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Eileen Bulger, M.D.
Co-Principal Investigator

Judy Powell, BSN
Project Director

Prehospital Tranexamic Acid Use for Traumatic Brain Injury (Prehospital TXA for TBI)

2015-4-3 Amendment 1.2 – Summary of Changes TXA Protocol Consent/Notification and Ancillary Study Informed Consent

Amendment 1.2 contains three changes with the primary TXA protocol and ancillary study entitled *Blood-Based Biomarkers of Injury and Outcome in the Prehospital TXA for TBI Trial*.

TXA Protocol Revision

1. On page 53 in Appendix 2 *Sample – Prehospital TXA Use for TBI Consent/Notification* under Study Procedures item #4 has been revised to read:

Tests in the future not yet known at this time (No genetic testing will be done for this study. We will ask for your consent to perform genetic testing at another time for a separate study.)

Rationale: The wording (*No genetic testing will be done at any time*) no longer accurately reflects the genetic sampling that will now be requested under the ancillary study.

Ancillary Study Revisions

2. In Appendix 3 Ancillary study, on page 69 Section D. Study Design and on page 77 in *Sample – Genetics Consent/Notification* under Purpose the study enrollment now states “approximately 1000 patients/subjects”.

Rationale: The new wording more accurately reflects the anticipated enrollment of 963 subjects and avoids the restrictiveness of the original wording “The study will enroll 1002 subjects...” This is explained in detail on page 73 under Sample size justification.

3. On page 79 under Confidentiality the wording that describes the Certificate of Confidentiality from the NIH has been added.

Rationale: On February 19, 2015 the NIH provided an amended Confidentiality Certificate to add the ancillary study with the informed consent/notification for genetic samples. (See letter from NIH below)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

2/19/2015

University of Washington
Dr. Susanne May
1107 NE 45th St.
Suite 505
Seattle, WA 98105

RE: CC-HL-14-13

Dear Dr. May,

Enclosed is the amended Confidentiality Certificate protecting the identity of research subjects in your project entitled, 'Prehospital Tranexamic Acid Use for Traumatic Brain Injury'. Please note that the amended Certificate expires on 09/29/2016.

This Certificate of Confidentiality is now amended to include corrections to the protocol and to add an ancillary study that has the same inclusion and exclusion criteria as the parent study.

If you determine that the research project will not be completed by the expiration date, 09/29/2016, you must submit a written request for an extension of the Certificate three months prior to the expiration date. Any such requests must include the reason for the request, documentation of the most recent IRB approval, and the expected date for completion of the research project.

Please advise me of any situation in which the Certificate is employed to resist disclosure of information in legal proceedings. Should attorneys for the project wish to discuss the use of the Certificate, they may contact the Office of the NIH Legal Advisor, National Institutes of Health, at (301) 496-6043.

Correspondence should be sent to:

Office of Clinical Research
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 8135
Bethesda, MD 20892
Telephone: (301) 594-4734
Fax: (301) 480-5845

Sincerely,

julie.mikulla@nih.gov

Digitally signed by
julie.mikulla@nih.gov
DN:
cn=julie.mikulla@nih.gov
Date: 2015.02.19 12:37:23
-05'00'

CERTIFICATE OF CONFIDENTIALITY

CC-HL-14-13A1

issued to

University of Washington

conducting research known as

Prehospital Tranexamic Acid Use for Traumatic Brain Injury

This certificate amends the certificate numbered CC-HL-14-13 issued on 06/03/2014.

In accordance with the provisions of section 301(d) of the Public Health Service Act 42 U.S.C. 241(d), this Certificate is issued in response to the request of the Principal Investigator, Dr. Susanne May, to protect the privacy of research subjects by withholding their identities from all persons not connected with this research. Dr. May is primarily responsible for the conduct of this research, which is supported by the National Heart, Lung, and Blood Institute grant number U01HL077863 and the U.S. Department of Defense.

Under the authority vested in the Secretary of Health and Human Services by section 301(d), all persons who:

1. are enrolled in, employed by, or associated with the University of Washington and their contractors or cooperating agencies and
2. have in the course of their employment or association access to information that would identify individuals who are the subjects of the research pertaining to the project known as Prehospital Tranexamic Acid Use for Traumatic Brain Injury

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research.

The primary aim of this study is to determine the efficacy of two dosing regimens of TXA initiated in the prehospital setting in patients with moderate to severe TBI (GCS score =12). The null hypothesis is that random assignment to prehospital administration of TXA in patients with moderate to severe TBI will not change the proportion of patients with a favorable long-term neurologic outcome compared to random assignment to placebo, based on the GOS-E at 6 months. The number of subjects needed to complete the study will be 1002 (334 per group) over all sites.

A Certificate of Confidentiality is needed because sensitive information will be collected during the course of the study. The certificate will help researchers avoid involuntary disclosure that could expose subjects or their families to adverse economic, legal, psychological and social consequences.

All subjects will be assigned a code number and identifying information and records will be kept in locked files at the Institution.

This research is currently underway and is expected to end on 09/29/2016.

As provided in section 301 (d) of the Public Health Service Act 42 U.S.C. 241(d):

'Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.'

This Certificate does not protect you from being compelled to make disclosures that: (1) have been consented to in writing by the research subject or the subject's legally authorized representative; (2) are required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) or regulations issued under that Act; or (3) have been requested from a research project funded by the National Institutes of Health (NIH) or the Department of Health and Human Services (DHHS) by authorized representatives of those agencies for the purpose of audit or program review.

CERTIFICATE OF CONFIDENTIALITY

CC-HL-14-13A1

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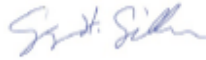
conducting research known as

Prehospital Tranexamic Acid Use for Traumatic Brain Injury

This certificate amends the certificate numbered CC-HL-14-13 issued on 06/03/2014.

This Certificate does not represent an endorsement of the research project by the DHHS. This Certificate is now in effect and will expire on 09/29/2016. The protection afforded by this Confidentiality Certificate is permanent with respect to subjects who participate in the research during the time the Certificate is in effect.

Date: 2/19/2015



Office of the Director

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Prehospital Tranexamic Acid Use for Traumatic Brain Injury (Prehospital TXA for TBI)

2015-07-29 Amendment 2* – Revised Protocol Summary of Changes

1. Section 5.2.3 In-hospital intervention – The window of time to start the in-hospital drug infusion has been changed from within 3 hours of arrival at hospital or completion of first drug infusion to within 6 hours.

Rationale: Data from CRASH II suggest that when TXA is given to trauma patients more than 3 hours after injury, there is an increased mortality. For this reason, the protocol previously stated that if the infusion is not begun within 3 hours of hospital arrival or 3 hours from completion of the prehospital infusion it will not be given. However, all patients who receive TXA in the hospital will have received a prior dose of 1 gram. There is no evidence that a second dose of TXA given more than 3 hours after the first results in increased morbidity and mortality. Therefore, in order to decrease protocol deviations and complete the protocol in a greater percentage of patients, we propose expanding the exclusionary in hospital criteria from 3 hours to 6 hours. Start time of in-hospital infusions will be tracked.

2. Section 5.8 Early Termination of Study Drug - This section was reformatted to have only one list of reasons for stopping which are applied to either the prehospital or hospital setting.

Rationale: The reason for this change was to eliminate unnecessary duplicate wording and to indicate continuity of care decision making from the prehospital setting to the hospital setting.

(See page 2 for the relevant sections described above)

***Note: Amendment 1.2 dated 2015-4-3 solely contained changes that pertained to the genetic sampling in the ancillary study entitled *Blood-Based Biomarkers of Injury and Outcome in the Prehospital TXA for TBI Trial* included in Appendix 3 of the protocol.**

5.2.3 In-hospital intervention

Research personnel will be responsible for obtaining the unique code identifier (ID) for the in-hospital blinded study drug vial that matches the prehospital study drug kit ID# randomization assignment by contacting the ROC Data Coordinating Center (DCC) by automated web based or phone system. The vial labeled with this unique code ID will be used to prepare the maintenance infusion appropriate for the randomization assignment of either 1 gm TXA 8 hour infusion or placebo 8 hour infusion. The maintenance infusion will be administered as soon as possible after arrival, and every effort will be made to begin administration within 3 hours of arrival or within 3 hours of completion of the pre-hospital infusion. If the infusion is not begun within ~~63~~ hours of hospital arrival or ~~63~~ hours from completion of the prehospital infusion, it will not be given, ~~based on data suggesting increased complications with delayed infusions.~~ If the prehospital bolus infusion is not complete by the time the patient arrives to the hospital, it will be allowed to completely infuse and the maintenance infusion will be hung after completion of the bolus infusion. The subject will continue to receive the study drug as assigned until: (1) the study drug has completed the infusion, (2) the subject is demonstrated to have a serum creatinine >2.0 mg/dL at any time during study drug infusion, (3) the subject has died, (4) the patient, patient's family member or legally authorized representative (LAR) withdraws from the trial, (5) the subject is determined to be pregnant or a prisoner, or (6) the subject develops a thrombotic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity. If the patient is considered to be in hemorrhagic shock and the primary treatment team determines TXA should be administered as part of a massive transfusion protocol or based on local standard of care, emergency unblinding of the treatment arm will be immediately available to the hospital physician. All additional hemostatic agents and blood products will continue to be administered based on the discretion of the individual provider and according to local standard of care and will be recorded. Patients who develop hemorrhagic shock after randomization will continue to receive local standard of care treatment. If the treatment team is treating the patient for hemorrhagic shock and local standard of care includes administration of TXA, emergency unblinding will be required. The hospital physician will contact the ROC DCC's automated unblinding web base or phone system to obtain the field treatment arm if there is a need for rapid emergency unblinding. This will also automatically notify staff at the ROC DCC and the site research personnel via email of the emergency unblinding. The decision to administer additional TXA based on the patient's randomized treatment arm will be based on clinician judgment.

5.8 Early Termination of Study Drug

When EMS personnel open the blinded study drug kit, the patient is enrolled and randomized and will be included in the primary statistical analysis if the study drug is connected to the patient's IV access. The study drug will be terminated by EMS or by hospital providers for any of the reasons below.

Prehospital:

- Prehospital provider suspects the patient has developed a thrombotic event (MI, ischemic stroke,) or seizure activity OR after hospital arrival the patient develops a thrombotic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity
- ~~The patient requires cardiopulmonary resuscitation (CPR)~~

In-hospital:

- The patient, patient's family member or legally authorized representative (LAR) withdraws from the study
- ~~The patient develops a thrombotic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity~~
- ~~The patient requires cardiopulmonary resuscitation (CPR)~~
- The patient is discovered to be pregnant
- A serum creatinine > 2.0 mg/dL is obtained
- The patient requires administration of Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates
- The patient is discharged from the hospital prior to completion of the 8 hour infusion

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Prehospital Tranexamic Acid Use for Traumatic Brain Injury

2013-9-13 Proposal for PRC
2013-9-23 Proposal for FDA IND – Revised Appendix 2
2013-10-24 FDA IND 119858 Approved
2013-11-4 Revised Protocol for FDA IND 119858
2014-1-6 PRC Approved
2014-2-3 First Revised Protocol for DSMB
2014-3-4 Second Revised Protocol for DSMB
2014-3-14 DSMB Approved
2014-5-23 DSMB Approved: Amendment 1- Revised Protocol and Ancillary Study
2014-9-9 Amendment 1.1
2015-4-3 Amendment 1.2
2015-07-29 DSMB Approved Amendment 2
ClinicalTrials.gov ID: NCT01990768



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TXA	Acronyms
AA	Arachidonic Acid
ABC	Assessment of Blood Consumption
ABC/2	ICH hematoma volume was measured on the initial head CT scan with the use of the ABC/2 method, in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness.
ACT	Activated clotting time
ADP	Adenosine diphosphate
AE	Adverse Event
AHA	American Heart Association
AIS	abbreviated injury score
AKI	Acute Kidney Injury
Alb	Albumin
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
AT III	Antithrombin
ATC	Acute Traumatic Coagulopathy
ATLS	Advanced Trauma Life Support
ATV	All Terrain Vehicle
AUC	Area Under the Curve
Auto	Autologous blood
BAT	Basophil Activation Test
BD	Base Deficit
bHCG	beta Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
C	Celsius
CaCl ₂	Calcium Chloride
CAT	Calibrated Automatic
CBC	Complete Blood Count
CCC	clinical coordinating center
CeTIR	Center for Translational Injury Research
CFR	Code of Federal Regulations
CI	confidence interval
CIHR	Canadian Institutes of Health Research
CO ₂	Carbon Dioxide
CPR	Cardio Pulmonary Resuscitation
CRASH-2	The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage
CRASH-3	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

CRIC	Cricothyrotomy
Cryo	Cryoprecipitate
CSF	Cerebral Spinal Fluid
CSV	Comma, separated values
CT	Computed Tomography
CTC	University of Washington Clinical Trial Center
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
DCC	Data Coordinating Center (ROC)
DCR	Damage Control Resuscitation
DDE	Distributed data entry
DICOM	Digital Imaging and Communication in Medicine
DNA	Deoxyribonucleic Acid
DNR	Do Not Resuscitate
DO	Direct Observation
DoD	Department of Defense
DPL	Diagnostic Peritoneal Lavage
DRS	Disability Rating Scale
DSMB	Data Safety Monitoring Board
DVT	deep venous thrombosis
EAC	Endogenous Acute Coagulopathy
EACA	Epsilon-aminocaproic acid
EC	Executive Committee
ED	Emergency Department
EDTA	Ethylenediaminetetraacetic acid
EFIC	Exception From Informed Consent
ELISA	Enzyme-linked immunosorbent assay
EM	Emergency Medicine
EMS	Emergency Medical Services
ETP	Endogenous thrombin potential
F	Fahrenheit
FAST	Focused Assessment for the Sonography of Trauma
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FTP	File Transfer Protocol
FWA	Federal Wide assurance
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GMP	Good Manufacturing Practices
GOS	Glasgow Outcome Score
GOS-E	Glasgow Outcomes Score Extended

GSW	Gun Shot Wound
h	hour
HCCC	UTHealth Clinical Coordinating Center
HCG	Human Chorionic Gonadotropin
Hct	Hematocrit
HD	Hemodialysis
HDCC	UTHealth Data Coordinating Center
Hes	Hespan
Hex	Hexpan
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
HS	Hemorrhagic Shock
HS	Hypertonic saline
Ht	Hypertonic
HTML	Hypertext Markup Language
HUI	Health Utilities Index
ICH	Intracranial Hemorrhage
ICP	Intracranial pressure
ICRH	Institute of Circulatory and Respiratory Health
ICU	Intensive Care Unit
ID	Identification
IDE	Investigational device exemption
IND	investigational new drug
INR	International Normalized Ratio
IO	intraosseous
IR	Interventional Radiology
IRB	Institutional Review Board
IRB	Internal Review Board
ISS	Injury Severity Score
i-Stat	i-STAT Point-of-care Testing
IT	Information Technology
IVH	Intraventricular Hemorrhage
IV	Intravenous
JTTS	Joint Theatre Trauma System
kg	kilograms
LAR	Legal Authorized Representative
LED	Light Emitting Diode
LR	Lactated Ringer's
LSI	Life Saving Intervention
LTI	Life-threatening Traumatic Injury

LY30	Clot Lysis time at 30 minutes
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mA	maximum Amplitude
MATTERS	Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study
MC	Management Committee
MCC	Motorcycle Crash
mg	milligrams
MI	Myocardial Infarction
min	minutes
mL	milliliters
mmHg	millimeters of mercury
MOF	Multiple Organ Failure
MP	microparticle
MR	Medical Record
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
MT	Massive Transfusion
MVC	Motor Vehicle Collision
NEMSIS	National EMS Information System
NHLBI	National Heart, Lung, Blood Institute
NIH	National Institute of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIRS	Near Infrared Spectroscopy
NS	Normal Saline
O2	Oxygen
OCCC	Oregon Health Sciences University Clinical Coordinating Center
OCTRI	Oregon Clinical and Translational Research Institute
ODBC	Open Database Connectivity
OHRP	Office for Human Research Protections
OHSU	Oregon Health Sciences University
OOH-CA	Out-of-hospital cardiac arrest
OPRR	Office for Protection from Research Risks
OR	Operating Room
PAP	Plasmin-Alpha-2-Antiplasmin
PAR	Protease-activated receptors
PCC	Prothrombin Complex Concentrate
PCR	Patient Care Record
PDF	Portable Document Format
PE	Pulmonary Embolism
PEST	Political, Economic, Social, and Technological Factors
PROPHET	Prospective Observational Prehospital and Hospital Registry for Trauma

PI	Principal Investigator
PI	Plasmalyte
PLT	Platelets
PMSF	phenylmethanesulfonyl fluoride
PRBC	packed red blood cells
PRC	ROC Protocol Review Committee
PROPHET	Prospective Observational Prehospital and Hospital Registry for Trauma
PROPPR	Pragmatic Randomized Optimal Plasma and Platelet Ratios
ProTECT	Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury
PT	prothrombin time
PTT	partial thromboplastin time
QL	Quality of life
RBC	Red Blood Cell
RCC	Regional Clinical Center
RCT	Randomized clinical trial
R&D	Research and Development
REB	Research Ethics Board (Canadian)
rFVIIa	Recombinant Factor VIIa
ROC	Resuscitation Outcomes Consortium
RR	relative risk
RT PCR	reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAH	Subarachnoid Hemorrhage
SAS	Statistical Analysis System Software
SBP	Systolic Blood Pressure
SC	Steering Committee
SCM	Steering Committee Meeting
sEPCR	soluble endothelial protein C receptor
SI	Surgical Intervention
SIR	Scientific Information Retrieval
SMC	Study Monitoring Committee
SPH	School of Public Health
SpO2	Saturation of Peripheral Oxygen
SPSS	Statistical Package for Social Sciences Software
SQL	Structured Query Language
SS	Special situations
SSH	Secure Shell
SSL	Secure Sockets Layer
sTM	soluble Thrombomodulin
StO2	Tissue Oxygenation

SUSAR	suspected unanticipated serious adverse reaction
TAFI	Thrombin-activatable fibrinolysis inhibitor
TBI	Traumatic Brain Injury
TBSA	Total Body Surface Area
TCCC	Tactical Combat Casualty Care
TEG	Thrombelastograph
TF	transfusion
TFPI	Tissue factor pathway inhibitor
TG	thrombin generation
TIC	Trauma Induced Coagulopathy
TP	Thawed Plasma
tPA	Tissue Plasminogen Activator
TRALI	Transfusion Related Acute Lung Injury
TRAP	Thrombin Receptor Activation Peptide
TRIO	Trauma Research Institute of Oregon
TXA	Tranexamic Acid
U	units
UCSD	University of California-San Diego
UCSF	University of California-San Francisco
ug	microgram
UK	United Kingdom
US	United States
USAMRMC	United States Army Medical Research and Materiel Command
UT Houston	University of Texas Health Sciences Center Houston
UTHealth	University of Texas Health Science Center-Houston
UW	University of Washington
UW-IT	University of Washington Information Technology
VAP	Ventilator assisted pneumonia
WBA	Whole Blood Aggregometry

SUMMARY

Prehospital Tranexamic Acid (TXA) Use for Traumatic Brain Injury (TBI)

Primary aim: To determine the efficacy of two dosing regimens of TXA initiated in the prehospital setting in patients with moderate to severe TBI (GCS score ≤ 12).

Primary hypothesis: The null hypothesis is that random assignment to prehospital administration of TXA in patients with moderate to severe TBI will not change the proportion of patients with a favorable long-term neurologic outcome compared to random assignment to placebo, based on the GOS-E at 6 months.

Secondary aims: To determine differences between random assignment to TXA and placebo in the following outcomes for patients with moderate to severe TBI treated in the prehospital setting with 2 dosing regimens of TXA:

- *Clinical outcomes:* ICH progression, Marshall and Rotterdam CT classification scores, DRS at discharge and 6 months, GOS-E at discharge, 28-day survival, frequency of neurosurgical interventions, and ventilator-free, ICU-free, and hospital-free days.
- *Safety outcomes:* Development of seizures, cerebral ischemic events, myocardial infarction, deep venous thrombosis, and pulmonary thromboembolism.
- *Mechanistic outcomes:* Alterations in fibrinolysis based on fibrinolytic pathway mediators and degree of clot lysis based on TEG.

Inclusion criteria: Blunt and penetrating traumatic mechanism consistent with TBI with prehospital GCS ≤ 12 prior to administration of sedative and/or paralytic agents, prehospital SBP ≥ 90 mmHg, prehospital intravenous (IV) access, age ≥ 15 yrs (or weight ≥ 50 kg if age is unknown), EMS transport destination based on standard local practices determined to be a participating trauma center.

Exclusion criteria: Prehospital GCS=3 with no reactive pupil, estimated time from injury to start of study drug bolus dose >2 hours, unknown time of injury, clinical suspicion by EMS of seizure activity, acute MI or stroke or known history, to the extent possible, of seizures, thromboembolic disorders or renal dialysis, CPR by EMS prior to randomization, burns $> 20\%$ TBSA, suspected or known prisoners, suspected or known pregnancy, prehospital TXA or other pro-coagulant drug given prior to randomization, subjects who have activated the "opt-out" process when required by the local regulatory board.

Study design and infusion period: A multi-center double-blind randomized controlled clinical trial with three treatment arms:

- *Bolus/maintenance arm:* 1 gram IV TXA bolus in the prehospital setting followed by a 1 gram IV maintenance infusion initiated upon hospital arrival and infused over 8 hours.
- *Bolus only arm:* 2 grams IV TXA bolus in the prehospital setting followed by a placebo maintenance infusion initiated upon hospital arrival and infused over 8 hours.
- *Placebo arm:* Placebo IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated upon hospital arrival and infused over 8 hours.

EMS agencies will carry blinded sealed study drug kits. Once the seal is broken in the presence of the patient, the patient is randomized. The EMS study drug kit will contain a vial of either 1 gram TXA, 2 grams TXA, or placebo. EMS will mix the study drug in a 250 mL bag of 0.9% sodium chloride and administer the bolus infusion as soon as life-saving interventions are performed. After randomization, EMS will provide the study drug kit ID# to research personnel upon arrival in the emergency department (ED). The research personnel will contact the study coordinating center and, using the kit ID#, obtain the unique code ID for the blinded study drug vial that matches the randomization assignment for the appropriate drug to be administered in the hospital.

Sample size: The total sample size in the primary analysis population is 963 (321 per group), which will allow for 80% power to detect a 7.1% absolute increase in the proportion of patients with a favorable long-term neurological outcome as determined by the GOS-E 6 months after injury comparing patients who receive TXA to patients who receive placebo, using a one-sided, level 0.1 test. It will allow for 80% power to detect an absolute decrease of 9.5% in the proportion of patients with a favorable long-term neurologic outcome comparing patients who receive TXA to patients who receive placebo, using a one-sided, level 0.025 test.

Statistical analysis of primary hypothesis: Modified intention-to-treat analysis using logistic regression to test for association and estimate the strength of the association of treatment group with a favorable 6-month outcome (defined as a GOS-E > 4), after adjustment for study site.

Human subjects protection: This study qualifies for the exception from informed consent (EFIC) required for emergency research outlined in FDA regulation 21CFR50.24. EFIC applies because of life-threatening situation, intervention must be administered before consent is feasible, no reasonable way to identify prospectively individuals at risk, patients have the prospect of benefit from the treatment, and the research could not practically be carried out without the waiver of consent.

1. Overview

This multi-center, Phase II trial is designed to determine if Tranexamic Acid (TXA) initiated in the prehospital setting improves long-term neurologic outcome compared to placebo in patients with moderate to severe TBI who are not in shock. This study protocol will be conducted as part of the Resuscitation Outcomes Consortium (ROC) at trauma centers in the United States and Canada. ROC is funded by the National Heart Lung and Blood Institute (NHLBI) in partnership with the US Army Medical Research and Materiel Command (USAMRMC), Canadian Institutes of Health Research, the Heart & Stroke Foundation of Canada, the American Heart Association (AHA), and the Defense Research and Development Canada. ROC is a clinical trials network focusing on research primarily in the area of prehospital cardiopulmonary arrest and severe traumatic injury. The mission of ROC is to provide infrastructure and project support for clinical trials and other outcome-oriented research in the areas of cardiopulmonary arrest and severe traumatic injury that lead to evidence-based change in clinical practice.

2. Specific Aims/Hypothesis Statement

2.1 Clinical Hypotheses and Aims

Specific aim 1: To compare 6-month neurologic outcome between patients who are randomly assigned to TXA to patients who are randomly assigned to placebo by evaluating the Glasgow Outcome Scale Extended score (GOS-E) at 6 months post-injury.

Primary Hypothesis: We will perform a one-sided test of the following null hypothesis:

- The proportion of patients who have a favorable neurologic outcome (GOS-E > 4) at six months post injury who are randomly assigned to TXA is not different from the proportion of patients who have a favorable neurologic outcome (GOS-E > 4) who are randomly assigned to placebo. This hypothesis will be tested versus the alternative that the proportion of patients with a favorable neurologic outcome who are randomly assigned to TXA is higher than in patients who are randomly assigned to placebo at the .1 level and versus the alternative that the proportion of patients with a favorable neurologic outcome who are randomly assigned to TXA is lower than it is in the placebo group at the .025 level

Specific aim 2: To assess differences in morbidity and mortality measured from randomization through 28 days or initial hospital discharge between subjects in the bolus/maintenance arm, bolus only arm, and placebo arm.

Secondary Hypotheses: The null hypotheses are that there will be no difference between patients who are randomly assigned to TXA and patients who are randomly assigned to placebo in the following: absolute and relative volume of intracranial hemorrhage (ICH) progression, proportion with ICH progression, Marshall and Rotterdam CT classification scores, frequency of neurosurgical interventions, GOS-E measured at discharge, Disability Rating Scale score (DRS) measured at discharge and 6 months, 28-day survival, and ventilator-free, intensive care unit (ICU)-free, and hospital-free days.

Specific aim 3: To assess differences in adverse events measured from randomization to initial hospital discharge between subjects in the bolus/maintenance arm, bolus only arm, and placebo arm.

Tertiary Hypotheses: The null hypotheses are that there will be no difference between patients who are randomly assigned to TXA and patients who are randomly assigned to placebo in the following: proportion of patients experiencing seizures, cerebral ischemic events, myocardial infarction (MI), deep venous thrombosis (DVT), or pulmonary thromboembolism (PE) post randomization through 28 days or discharge, whichever occurs first.

2.2 Laboratory Hypotheses and Aims

Specific aim 1: To compare coagulation profiles over time using kaolin activated thrombelastography (TEG) results between patients who are randomly assigned to TXA and patients who are randomly assigned to placebo.

Primary hypothesis: The null hypothesis is that there will be no difference in the degree of fibrinolysis as assessed by percentage of clot lysis determined 30 minutes after the maximum amplitude is reached (LY30) between patients who are randomly assigned to TXA and patients who are randomly assigned to placebo.

Specific aim 2: To explore the underlying mechanism of TXA by comparing fibrinolytic pathway mediator activity between patients who receive TXA and patients who receive placebo.

Secondary hypothesis: The null hypothesis is that there will be no change in fibrinolytic pathway mediators between patients who are randomly assigned to TXA and patients who are randomly assigned placebo.

Specific aim 3: To estimate the association between the degree of fibrinolysis based on kaolin activated TEG results and fibrinolytic pathway mediators on primary and secondary clinical outcomes.

Tertiary hypothesis: The null hypothesis is that no association will exist between the degree of fibrinolysis based on TEG and fibrinolytic pathway mediators (listed in specific aim 2) and primary and secondary clinical outcomes.

3. Background

3.1 Traumatic Brain Injury

3.1.1 Epidemiology of traumatic brain injury

TBI is the leading cause of death and disability due to trauma and is the number one cause of death in people younger than 40 years old.¹ Every year, more than 1.6 million people sustain a TBI resulting in 80,000 permanent severe neurological disabilities and 52,000 deaths.^{2,3,4} TBI is responsible for the greatest number of potential years of life lost from any cause and the highest burden on quality adjusted life years lost in survivors.⁵ Current evidence and clinical guidelines emphasize the importance of early and effective hemodynamic resuscitation following TBI and stress the deleterious effects of hemorrhagic shock complicating TBI.⁶ Mortality in patients with severe TBI is greater than 25%⁷ yet one third of patients still survive with minimal to moderate neurologic deficits. Given this wide variability in neurological recovery, an effective treatment for TBI has the potential to significantly impact neurologic outcomes.

TBI has been labeled as the signature wound of the Iraq/Afghan conflict. The number of military personnel that have suffered blunt TBI has risen dramatically due to an increase in concussive weapons and a decrease in penetrating injury as a result of improved armor. Approximately 20% of combat personnel have suffered a TBI while in theater,⁸ and this estimate is likely conservative as there is limited in-field screening. Despite the significant impact that TBI has on both the military and civilian populations, there remains no effective pharmacological agent that has been shown to improve outcome for TBI.^{8,9,10,11} A review of five treatments (hyperventilation, mannitol, cerebral spinal fluid drainage, barbiturates, corticosteroids) for TBI found that when studies were properly controlled, none of these treatments were shown to be effective for reducing morbidity and mortality.¹² No new pharmacological therapy has been implemented for routine use in acute TBI in over 30 years.¹²

3.1.2 Secondary traumatic brain injury – coagulation and progression of intracranial hemorrhage

In patients with TBI, the extent of the brain damage is determined by the severity of the primary mechanical injury as well as the degree of secondary brain injury. Thus, the management of TBI focuses on limiting secondary brain injury. Coagulopathy has been recognized as a major factor contributing to secondary brain injury and worse outcome after TBI.¹³ The mechanism for coagulopathy after TBI has been studied extensively but remains unclear. Patients with TBI are at risk for developing abnormalities of both coagulation and fibrinolysis.¹⁴ There is evidence that the extent of injured brain tissue correlates with the degree of coagulopathy.¹⁵ In 1974 Goodnight et al. hypothesized that tissue thromboplastin released from damaged brain, also known as tissue factor, enters the circulation, activates the extrinsic coagulation pathway, and produces fibrin clot.^{16,17} Tissue factor is considered the primary initiator of coagulation and its release can activate the coagulation system excessively in patients with head trauma.¹⁸ Additional proposed mechanisms involve abnormalities in the fibrinolytic system as well as depletion of platelets and clotting factors following blood loss or consumption from disseminated intravascular coagulation.¹⁹ A more recent hypothesis suggests that TBI alone does not cause early coagulopathy but must be coupled with hypoperfusion to lead to coagulation derangements associated with the activation of the protein C pathway.²⁰

Overall, up to 50% of patients with TBI develop progression of ICH as evidenced by a new or progressive lesion on repeat head computed tomography (CT) scan.²¹ Eighty-five percent of patients with at least one abnormal routine coagulation test will develop progression of ICH, yet even in patients with normal coagulation assays, 1/3 of patients will still develop progression.²¹ The correlation between routinely collected coagulation tests and progression of ICH remains controversial. Stein et al. demonstrated that an abnormal International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), and platelet count independently correlated with progression of injury.²¹ Oertel et al. showed only the aPTT correlated with injury progression²² while Schnuriger et al. showed that decreased platelet counts (though still within the normal range) were associated with increased ICH progression.²³ While the relative impact of individual clotting abnormalities on progression of ICH continues to be the subject of debate, it is clear that patients with demonstrated coagulopathy after TBI have a significantly increased rate of ICH progression compared to those without coagulopathy.²⁴ Since progression of ICH is independently associated with increased need for surgical intervention, decreased long-term neurologic outcome, and a 5-fold increase in mortality,²¹ an early intervention that could decrease the development of progressive ICH could theoretically have a major impact on patient outcome.

3.1.3 Secondary traumatic brain injury – inflammation and development of cerebral edema

The development of cerebral edema is another important type of secondary brain injury. It is clear that the formation of cerebral edema is a major factor leading to the high morbidity and mortality in patients with TBI.²⁵ No new treatments have been developed in recent years that are effective at reducing cerebral edema, in part because the mechanism is only recently becoming better understood. Cerebral edema occurs by the addition of water from the vasculature (vasogenic edema), whereas cytotoxic edema results from a shift of water from the extracellular to the intracellular compartment. Thus, the primary focus of research involving cerebral edema is directed toward attenuating the permeability of the blood brain barrier. It is well established that systemic inflammation is common after major trauma and TBI. It is becoming increasingly recognized that multiple classes of inflammatory mediators can lead to increased permeability of the blood brain barrier and the development of cerebral edema.²⁶ In a frontal cortex contusion model, a marked inflammatory reaction was observed after injury in both the injured region and surrounding areas of the brain.²⁷ This model also demonstrated an invasion of macrophages and neutrophils into the area of impact with increased inflammatory cytokine generation.²⁷ With the aid of novel magnetic resonance imaging techniques, vasogenic edema has been shown to occur within a few hours after injury.²⁸ Thus, the development of a neuroprotective agent that could be given very early after injury, before edema develops, could have a major impact on morbidity and mortality in patients with TBI.

3.2 Overview of Hemostasis

Hemostasis requires a balance between the coagulation cascade responsible for producing fibrin clot and the fibrinolytic system that dissolves fibrin clot. At sites of tissue injury, activation of the coagulation cascade results in thrombin formation, which cleaves fibrinogen to fibrin monomers. These monomers polymerize to form fibrin that seals the damaged vessel wall. This deposition of fibrin then activates the fibrinolytic system to help maintain the patency of the vessel lumen. Fibrinolysis occurs when plasminogen, which is trapped within the clot, binds to lysine residues on the surface of the fibrin. When a plasminogen activator is present (like tissue plasminogen activator [tPA]), plasminogen is converted to plasmin, which then degrades fibrin into fragments that are further broken down and removed from circulation. Fibrinolysis is regulated by plasminogen activators (tPA), plasminogen activator inhibitors (plasminogen activator inhibitor-1 [PAI-1]), and plasmin inhibitors (α -2 antiplasmin), and is affected by the rapid hepatic clearance of these molecules. Excessive breakdown of fibrin (hyperfibrinolysis) results in excessive bleeding and has been associated with a wide variety of conditions ranging from perioperative blood loss to subarachnoid hemorrhage.²⁹ Hyperfibrinolysis has been associated with significantly increased mortality after major trauma.³⁰ Antifibrinolytics such as TXA and aminocaproic acid can inhibit hyperfibrinolysis by interfering with plasmin production, thus stabilizing the fibrin clot.

3.3 TXA

3.3.1 FDA indications for TXA

In January 2011, the US Food and Drug Administration (FDA) approved the injection formulation of TXA (NDA 019281, branded Cyklokapron) 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, with a revised label warning to include convulsions (and no change to the indications). The FDA has approved TXA injection as a therapeutically equivalent generic drug that is available from X Gen Pharmaceuticals Inc (NDC 39822-1000-1). Because of the planned off-label use of the drug as a bolus dose and 8-hour maintenance infusion for TBI in a prehospital federally funded trial using exception from informed consent for emergency research, the drug will require Investigational New Drug exemption in accordance with federal regulations.

3.3.2 Previous use of TXA

Clinical use of TXA was first described in 1966.³¹ TXA is a synthetic derivative of the amino acid lysine that acts by competitively inhibiting plasminogen activation and at higher concentrations, noncompetitively inhibiting plasmin.³² TXA binding blocks the interaction of plasminogen with fibrin preventing breakdown of fibrin clot. Thus, rather than promoting new clot formation, it prevents clot breakdown. While plasminogen may still be converted to plasmin in the presence of a plasminogen activator, after binding TXA, plasmin can no longer bind fibrin.³² TXA also blocks the binding of α -2 antiplasmin to plasmin and thus prevents its inactivation of plasmin.³² The use of TXA to control bleeding has been described in a number of clinical settings including, pediatric urinary tract surgery,³³ ruptured intracranial aneurysms,³⁴ oral surgery,³⁵ gynecologic surgery,³⁶ treatment of hereditary angioneurotic edema,³⁷ upper gastrointestinal hemorrhage,³⁸ traumatic hyphema,³⁹ hemophilia,⁴⁰ von Willebrand disease, and refractory thrombocytopenia.⁴¹ More recently, TXA has been adopted to treat hyperfibrinolysis associated with cardiopulmonary bypass and liver transplantation and has been shown to decrease both blood loss and need for transfusion.⁴²

The use of TXA in patients with neurological disease including subarachnoid hemorrhage dates back to the 1980's.⁴³ Intracranial aneurysm rupture results in bleeding into the subarachnoid space and subsequent brain damage due to destruction of brain parenchyma, increased intracranial pressure, mid-line shift and ultimate herniation. Of patients that survive, 20% develop re-bleeding with delayed ischemic deficits.^{44,45} In a randomized, placebo-controlled, double-blind study in 478 patients with spontaneous subarachnoid hemorrhage, a significant reduction in the rate of re-bleeding was demonstrated (9% TXA versus 24% placebo), however overall outcome was not improved due to an increase in the incidence of cerebral

ischemia.⁴³ Due to the lack of effect on mortality, the use of TXA was not recommended in this population.⁴⁶ However, in a later study using lower doses of TXA in patients with spontaneous subarachnoid hemorrhage, TXA was again observed to decrease acute re-bleeding, with no increase in ischemic complications.⁴⁷ One important difference in studies that have demonstrated increased cerebral ischemic events is the use of prolonged dosing regimens (3-4 times per day for 2-8 days), similar to its use in hemophilia. The more recent large studies that demonstrate no increase in cerebral ischemia have utilized a shorter duration, similar to the dosing proposed in this study.⁴⁸

The FDA approved label for tranexamic acid (TXA) contraindicates the use of the drug in patients with subarachnoid hemorrhage noting that cerebral edema and cerebral infarction may even be caused by TXA in such patients. In this study TXA will be administered to patients during the prehospital intervention phase and prior to obtaining any brain imaging results. Subarachnoid hemorrhage (SAH) is known to occur commonly in patients with traumatic brain injury, including those with penetrating injuries. Early studies examining the use of TXA in SAH that used higher doses and longer duration of administration initially raised the concern that there may also be an increase in cerebral ischemia. In more recent studies that have used lower doses of TXA (similar to our trial), a significant decrease in the rate of rebleeding continues to be observed with no increase in cerebral ischemic events and improved long-term outcome. In a randomized trial including over 500 patients who received 1 gm TXA IV followed by 1 gm q 6 hours until the aneurysm was occluded, there was no evidence of a higher risk of ischemia.⁴⁹ Other smaller studies support this finding. A recent Cochrane review published in August 2013 examined this issue and while they concluded that the evidence does not support the use of antifibrinolytic drugs in the treatment of people with aneurysmal subarachnoid hemorrhage, this meta-analysis demonstrated a high degree of heterogeneity (including combining higher dosing regimens with lower dosing regimens, prolonged drug administration with short term administration, and older studies with newer studies using neuroprotection).⁵⁰ When subgroup analyses were performed specifically focusing on studies using superior methods to confirm ischemia (CT or autopsy), studies incorporating a placebo arm, and those utilizing neuroprotection, no significant differences were observed. Antifibrinolytic therapy had no effect on the rate of hydrocephalus. Thus, the Cochrane reviewers concluded that results of short-term treatment (as in our protocol) are promising and further randomized trials evaluating short-term antifibrinolytic treatment are needed.

3.3.3 Military and civilian experience with TXA and trauma

The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERs) was an observational study of 896 patients admitted to a Role 3 United Kingdom (UK) combat support hospital in Afghanistan between 2009-2010 who received at least 1 unit of packed red blood cells (PRBC) within 24 hours of admission.⁵¹ In this prospective cohort, 293 patients non-randomly received TXA. The TXA group had significantly lower mortality (17.4% versus 23.9%) despite being more severely injured. While a clear benefit was observed in patients who received a massive transfusion, the TXA group had a greater degree of blast injury and lower Glasgow Coma Scale score (GCS) on admission. Furthermore, the mortality difference was not apparent until 48 hours after admission, suggesting that a mechanistic benefit exclusive of its effects on coagulation may exist. Since this was an observational study, no blood was available for examination of the mechanism involved. Nonetheless, the results of this study were compelling and resulted in a change in the use of TXA in the UK and US. The US Joint Theater Trauma System Clinical Practice Guideline for Damage Control Resuscitation in deployed surgical hospitals now recommends that administration of TXA “as soon as possible after injury (but ideally not later than 3 hours post injury) should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage.”⁵²

The safety and efficacy of using TXA in trauma patients was recently studied in a large placebo-controlled trial of 20,211 trauma patients in 40 countries called “The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage” (CRASH-2).⁵³ Patients were considered eligible if they were within 8 hours of injury and had a (SBP) < 90 mmHg and/or heart rate > 110 beats per minute, or were considered to be at risk for significant hemorrhage. The ultimate decision to enroll eligible patients was based upon the uncertainty principle,

meaning that the physician had to be substantially uncertain about whether or not the patient would benefit from TXA to enroll them. Patients were randomized to either 1 gram TXA loading dose over 10 minutes followed by 1 gram TXA over 8 hours, or placebo. The primary outcome of the study was in-hospital death within 4 weeks of injury. The secondary outcomes were vascular occlusive events, transfusions, and surgical interventions. The treatment and placebo groups were well matched. The all-cause mortality rate was significantly reduced in the TXA group compared to the placebo group (14.5% versus 16%). Interestingly, there was no difference in the number of blood products transfused between groups, calling into question the underlying mechanism for the observed benefit and raising the question as to which patient population benefitted from TXA. Because of the broad trauma patient population in CRASH-2, several pre-specified analyses of the data have been performed. In one post-hoc analysis of the CRASH-2 trial data, the association between time of administration of TXA and death due to bleeding as an end-point (as opposed to all-cause mortality) was evaluated.⁵⁴ In this analysis, the authors demonstrated that death due to bleeding was dependent on the time from injury to treatment. When TXA was administered immediately after injury the relative risk (RR) of death due to bleeding was 0.61 (95% confidence interval [CI] 0.50-0.74) and progressively increased the later the drug was given. Patients who received TXA within one hour of injury had a 13% lower all-cause mortality (95% CI 0-25%) than those treated with placebo. When treatment was given beyond 3 hours from injury, however, the RR of death increased to 1.44 (95% CI 1.12-1.84) demonstrating a harmful effect. While these data clearly suggest that TXA should be given early after injury, the reason for the increased mortality at later time points remains unclear.

The results from CRASH-2 raised the possibility that TXA may also be effective in TBI. CRASH-2 did not exclude patients with TBI, however they did not report detailed outcomes for this cohort. To further examine the use of TXA in TBI, the investigators presented the results on a cohort of 270 patients with TBI (defined as brain CT compatible with TBI and GCS $\leq$ 14) who were enrolled in CRASH-2. The study was prospective with detailed CT data and pre-specified outcomes.⁴⁸ The primary outcome of the study was growth of the ICH, measured using CT at hospital admission and 24-48 hours later. Secondary outcomes were death from any cause, dependency (measured using the 5-point Modified Oxford Handicap Scale, dichotomized into dead or dependent versus independent) the need for neurosurgical intervention, and the appearance of new focal cerebral ischemic lesions on follow-up CT.^{53,55} In this analysis, the mean total hemorrhage volume growth was reduced from 8.1 ml in the placebo group to 5.9 ml in the TXA group. Equally important, however, was the finding that patients in the TXA group developed fewer new focal cerebral ischemic lesions than in the placebo group (4.9 versus 9.5%) and fewer patients died in the TXA group than in the placebo group (10.5 versus 17.5%). Since none of these results were statistically significant, however, the authors concluded that neither moderate benefit nor moderate harm of TXA in TBI could be excluded.

A second randomized controlled trial in patients with isolated TBI demonstrated similar trends. This trial was conducted in 240 patients with moderate to severe TBI who had a head CT with no immediate indication for surgery within 8 hours of injury.⁵⁶ Subjects were randomized to a 2 gram TXA bolus or placebo. The primary outcome was progressive ICH on repeat CT scan which was defined as greater than 25% increase in any dimension or the presence of a new hemorrhage. Progressive ICH was present in 14% of patients receiving TXA and 25% of patients receiving placebo. This trial also found reductions in ICH growth (RR=0.6; 95% CI 0.34-1.32) with TXA but did not collect data on ischemic lesions. The RR of death from all causes was 0.67 (0.34-1.32) in patients allocated to TXA compared to placebo, and no evidence of increased thromboembolic adverse events was observed in the TXA group. Due to the lack of significance, the authors concluded that further clinical trials are needed to assess the effect of TXA on death and disability in patients with TBI. A meta-analysis of these two trials demonstrated significant reduction in both hemorrhage growth (RR=0.72; 95% CI 0.55 to 0.94) and mortality (RR=0.63; 95% CI 0.40 to 0.99) with the use of TXA.⁵⁷

3.3.4 CRASH-3 trial

Based on the promising results from the two previous trials of TXA in TBI, the Tranexamic Acid for the Treatment of Significant Traumatic Brain Injury trial (CRASH-3) was designed to provide evidence concerning the effect of TXA on mortality and disability in patients with TBI.⁵⁷ The CRASH-3 trial is an international,

multicenter randomized double-blind placebo controlled trial. To be eligible for this study, patients must be within 8 hours of injury and have evidence of an ICH on CT scan or a GCS ≤ 12 , with no evidence of significant extracranial bleeding. The primary outcome is in-hospital death within 28 days.⁵⁷ This trial is currently underway but as in CRASH-2, will again utilize the uncertainty principle, such that patients will only be enrolled when the physician is substantially uncertain if TXA is indicated to treat the TBI. Furthermore, the investigators are allowing subjects to be enrolled up to 8 hours after injury and they do not plan to study the mechanisms by which TXA affects outcome after TBI.

3.3.5 Potential mechanisms of TXA

No studies have examined the mechanism of TXA in patients with TBI. CRASH-2 was a phase III study that was not preceded by a phase II study to evaluate the mechanism by which subjects may have benefitted from the drug.⁵³ No blood was collected and the effect of TXA using coagulation or fibrinolytic assays was not evaluated. Since there was no difference in the transfusion requirements between the TXA and the placebo groups, the mechanism leading to the mortality benefit in this trial remains in question. In the MATTERS study, TXA use was associated with significantly lower mortality; however, the mortality difference was not apparent until 48 hours after admission suggesting an alternate mechanism instead of a coagulation effect may be dominant.⁵¹ In this trial, as in CRASH-2, there was no assessment of fibrinolysis or the effect of treatment on fibrinolysis.

Several potential mechanisms may be responsible for the lower mortality and reduction in ICH growth observed in previous studies. Increased fibrinolysis, as measured by elevated fibrinogen degradation products and D-dimers, is a common finding in the coagulopathy associated with TBI,⁵⁸ thus raising the possibility that TXA may exert an effect by limiting progression of ICH through its antifibrinolytic activity. Another mechanistic explanation is that TXA may act by reducing the neurotoxic or proinflammatory effects of plasmin, independent of its effect on hemostasis.⁵⁹ Tissue plasminogen activator has been shown to be important in the development of cerebral edema in the injured brain, presumably by activating plasminogen to plasmin.^{60,61,62} By blocking the conversion of plasminogen to plasmin, TXA may potentially counteract the effect of tPA resulting in decreased cerebral edema. A third potential mechanism is related to the interaction between the inflammatory and coagulation systems. Hyperfibrinolysis has been associated with inflammatory states and the generation of proinflammatory cytokines.⁶³ By preventing hyperfibrinolysis, TXA may lead to decreased expression of proinflammatory cytokines. Several recent studies have demonstrated that TXA decreases inflammation in cardiac surgery,^{64,65} however, the pro- and anti-inflammatory effects of TXA have not yet been investigated in trauma patients with TBI.

3.3.6 Limitations of existing evidence:

There are several limitations of the currently available evidence that underscore the need for additional well-designed trials in clearly defined patient populations. First, there is limited applicability of the currently available evidence for countries with well-developed trauma systems. Almost all of the patients enrolled in CRASH-2 were from low and middle-income countries. In these countries transfusion protocols utilizing blood component therapy are rarely available. Furthermore, a majority of these countries lack the well-developed trauma systems with advanced prehospital care that is available in the United States. Trauma system improvements, including advanced prehospital care and rapid access to surgical intervention, have significantly improved both functional recovery and survival after injury in developed countries. This difference in resources between under-developed and developed trauma systems also limits the applicability of the safety analysis in CRASH-2. While no apparent increase in vascular occlusive events in patients treated with TXA compared to placebo was observed, it is possible that pro-thrombotic risks not identified in CRASH-2 might be demonstrated in the United States given the increased use of plasma and platelets. Furthermore, screening protocols for these events are utilized more frequently in the United States than they were in the CRASH-2 sites. Additionally, the trial design utilizing the uncertainty principle employed in CRASH-2 (and currently being utilized in the CRASH-3 trial) resulted in an ill-defined patient population, further limiting the generalizability and reproducibility of the results. Thus, it still remains unclear exactly which patient populations should receive TXA. Finally, the

mechanism of TXA in patients with TBI remains unknown since neither the CRASH-2 trial or the MATTERs study performed mechanism related laboratory assays. This knowledge is critical to better understand the effect of TXA on coagulation, fibrinolysis, and inflammation in order to interpret the results of this trial. This information will be used to direct future studies to evaluate drugs that target pathways not affected by TXA and to provide important information related to differences that may be observed between this trial and CRASH-2. Despite these limitations, the currently available data for the use of TXA in injured patients is compelling and mandates well designed large randomized clinical trials in injured patients to further define the risks and benefits of TXA in both shock and TBI.

4. Trial Design

4.1 Setting

4.1.1 Resuscitation Outcomes Consortium

The ROC is a research network of North American Emergency Medical Systems and level one trauma centers (10 regional clinical centers and 7 satellite centers)⁶⁶ and a single data coordinating center (DCC). Since its inception in 2004, ROC has provided infrastructure and project support for clinical trials and outcome-oriented research in the areas of cardiopulmonary arrest and severe traumatic injury. ROC has been able to leverage the vast collective resources of its member institutions and promote the rapid translation of scientific advances for public good. The proposed randomized clinical trial reflects the growth and extension of ROC's successful trauma research program from prehospital resuscitation interventions to interventions within the hospital environment. This trial will use the ROC infrastructure to implement the protocol as well as to provide additional funding.

4.1.2 ROC site selection

8 sites have committed to participate in this study based on the following criteria:

Site requirements:

- Emergency medical services (EMS) agency commitment to administer study drug
- 24/7 research coordinator for bedside data collection, blood draw, and notification of study enrollment and consent for continued participation
- Ability to obtain head CT scan as soon as possible after arrival and repeat head CT scan within 24 hours
- 24/7 capability of performing TEG
- 24/7 neurosurgical capability
- anticipated enrollment of ≥ 10 patients per month based on past experience

A minimum of 10 level one trauma hospitals within the ROC network of regional and satellite clinical sites will participate based on high enrolling performance in previous ROC trauma studies and completeness of site materials needed for application submission. The sites are as follows:

University of Alabama at Birmingham, Birmingham, AL; University of Texas Southwestern Medical Center, Dallas, TX; University of Washington Harborview Medical Center, Seattle, WA; Oregon Health & Science University, Portland, OR; St. Michael's Hospital, Toronto, CAN; Medical College of Wisconsin, Milwaukee, WI; University of Texas Health Sciences Center, Houston, TX; University of Cincinnati, Cincinnati, OH

4.2 Methods and Techniques

4.2.1 Objectives

This will be a phase II multi-site, randomized double-blind placebo controlled trial evaluating the efficacy and safety of TXA administered in the prehospital setting in subjects with moderate to severe blunt and penetrating TBI (GCS ≤ 12) who are not in shock (SBP ≥ 90 mmHg). The primary outcome will be the proportion of subjects with a favorable neurologic outcome (defined as a GOS-E > 4) six months after injury. The secondary outcomes will be volume of ICH progression, proportion of subjects with ICH progression, frequency of neurosurgical interventions, GOS-E measured at discharge, DRS measured at discharge and six months, 28-day survival, and ventilator-free, ICU-free, and hospital-free days. Safety will be assessed by evaluating the proportion of subjects experiencing cerebral ischemic events, MI, DVT, PE, and seizures measured from randomization through 28 days or discharge, whichever occurs first. Mechanistic endpoints including coagulation and fibrinolytic profiles will be examined to comprehensively characterize coagulation and provide insight into dynamic changes and their relationship to treatment and outcome. Additional blood will be collected and stored for future analysis of inflammatory markers.

4.3 Inclusion Criteria

Subjects must meet ALL of the following:

1. Blunt or penetrating traumatic mechanism consistent with traumatic brain injury
2. Prehospital GCS score ≤ 12 at any time prior to randomization and administration of sedative and/or paralytic agents
3. Prehospital SBP ≥ 90 mmHg prior to randomization
(SBP < 90 mmHg has been used as the entry criteria for nearly all major investigations studying the treatment of shock.^{67,68,69,70} Furthermore, prehospital hypotension has been associated with a dramatic increase in morbidity and mortality following severe TBI including a two-fold increase in the incidence of severe disability and death.⁷¹)
4. Prehospital intravenous (IV) access
5. Estimated Age ≥ 15 (or estimated weight > 50 kg if age is unknown)
(Enrollment will be restricted to age ≥ 15 years or > 50 kg if age is unknown as these adolescents are of appropriate size to receive the full dose of TXA).
6. EMS transport destination based on standard local practices determined to be a participating trauma center
(Patients who are temporarily stabilized at an outside facility and transported to a participating center will be considered 'modified scene patients' and will remain eligible if all other inclusion and exclusion criteria are met).

4.4 Exclusion Criteria

Subjects are ineligible if they meet any of the following:

1. Prehospital GCS=3 with no reactive pupil
2. Estimated time from injury to start of study drug bolus dose > 2 hours
3. Unknown time of injury - no known reference times to support estimation
(In the CRASH-2 trial when treatment was given beyond 3 hours from injury the RR of death increased to 1.44 (95% CI 1.12-1.84) demonstrating a harmful effect.)
4. Clinical suspicion by EMS of seizure activity, acute MI or stroke, or known history, to the extent possible, of seizures, thromboembolic disorders or renal dialysis
5. CPR by EMS prior to randomization
6. Burns $> 20\%$ total body surface area (TBSA)
7. Suspected or known prisoners (Defined as any individual involuntarily confined or detained in a penal institution or any individual in police custody who must have a police escort at all times and excluded due to their vulnerable population status.)

8. Suspected or known pregnancy – (Since there are no well controlled studies in pregnancy, women who are either known or suspected to be pregnant will be excluded. However, data regarding the use of TXA in pregnant women are available demonstrating no thrombogenic effects of TXA in a retrospective analysis of 256 women with bleeding disorders in pregnancy.⁷² No mutagenic activity of TXA has been shown in vitro or in vivo test systems^{73,74} and no fetal abnormalities were identified in early dysmorphology and reproductive studies in animals.^{75,76})
9. Prehospital TXA or other pro-coagulant drug given prior to randomization
10. Subjects who have activated the “opt-out” process when required by the local regulatory board.

5. Intervention

5.1 Screening Procedures

Screening will be conducted in the prehospital setting by the initial EMS responder. Prehospital trauma life support interventions focusing on airway, breathing and circulation will be performed and an initial GCS score will be assessed by EMS to determine eligibility. The patient will be considered eligible if the initial GCS is ≤ 12 and the SBP has remained ≥ 90 mmHg prior to randomization, and other inclusion/exclusion criteria are met. If the GCS improves to greater than 12 prior to randomization, the patient will not be randomized. If the initial GCS is > 12 and during transport declines to ≤ 12 prior to administration of sedating and/or paralytic medication, the patient will become eligible if the SBP has remained ≥ 90 mmHg prior to randomization. If the SBP drops below 90 mmHg between randomization and administration of study drug or anytime thereafter, the patient will remain in the study and continue to receive the study drug.

5.2 Study Procedures

5.2.1 Randomization

Eligible patients will be randomly allocated in a proportion of 1:1:1 bolus/maintenance arm, bolus only arm, and placebo. Randomization assignments will be generated by the ROC DCC. To attempt balance by site, permuted blocks of varying concealed size will be used. Nevertheless, location of the episode and availability of providers determine which agency responds to the episode and the order in which the containers are used cannot be determined a priori. As a result, the randomization will represent a complete randomization rather than a permuted block randomization.

5.2.2 Prehospital intervention

Participating EMS vehicles will carry pre-randomized, sealed, numbered containers of study drug. After confirming the patient meets criteria for entry into the study, participating EMS providers will open the study drug kit on their vehicle. Patients are considered randomized if a study drug kit seal is broken in the presence of the patient based on the above screening criteria even if the drug is not administered. EMS providers will be instructed to obtain intravenous (IV) access prior to opening the study drug kit. Vascular access and fluid administration will be per standard protocol by the EMS agency. EMS will mix the drug and administer the bolus infusion as soon as life-saving interventions are performed. If IV medication in addition to TXA is required and only one IV access line is available, EMS will be instructed to clamp the IV tubing, flush the line with 10 ml saline, give the emergency drug IV push, flush the line again with 10 ml saline, and resume the TXA infusion. If the bolus infusion is stopped for reasons other than a protocol violation or a serious adverse event that may be associated with TXA, it is to be restarted and completed within 3 hours of the estimated time of injury either prior to ED arrival or after ED arrival and the in-hospital study drug infusion will be given. If it is anticipated that the bolus infusion cannot be completed within 3 hours of the estimated time of injury then it will not be resumed and the in-hospital study drug infusion will not be given.

After randomization, EMS will provide the kit ID# to research personnel upon arrival in the receiving ED. The research personnel will contact the study coordinating center and, using the kit ID#, obtain the unique code ID for the blinded study drug vial that matches the randomization assignment for the appropriate hospital infusion administration. In the rare case that the patient is brought to a non-participating facility, all study interventions will stop, the patient or patient's family member or legally authorized representative (LAR) will be informed that they were enrolled in the study and asked to give permission to obtain their medical information so they may be followed for primary and safety endpoints. In order to avoid this event, patients will only be eligible for this study if a determination is made that their destination is a participating hospital. This determination is made independent of the study and is based on standard local practices. Therefore, enrollment in the study will not delay transport to the participating hospital with the exception of any delay related to administering the drug.

5.2.3 In-hospital intervention

Research personnel will be responsible for obtaining the unique code identifier (ID) for the in-hospital blinded study drug vial that matches the prehospital study drug kit ID# randomization assignment by contacting the ROC Data Coordinating Center (DCC) by automated web based or phone system. The vial labeled with this unique code ID will be used to prepare the maintenance infusion appropriate for the randomization assignment of either 1 gm TXA 8 hour infusion or placebo 8 hour infusion. The maintenance infusion will be administered as soon as possible after arrival, and every effort will be made to begin administration within 3 hours of arrival or within 3 hours of completion of the prehospital infusion. If the infusion is not begun within 6 hours of hospital arrival or 6 hours from completion of the prehospital infusion, it will not be given. If the prehospital bolus infusion is not complete by the time the patient arrives to the hospital, it will be allowed to completely infuse and the maintenance infusion will be hung after completion of the bolus infusion. The subject will continue to receive the study drug as assigned until: (1) the study drug has completed the infusion, (2) the subject is demonstrated to have a serum creatinine >2.0 mg/dL at any time during study drug infusion, (3) the subject has died, (4) the patient, patient's family member or legally authorized representative (LAR) withdraws from the trial, (5) the subject is determined to be pregnant or a prisoner, or (6) the subject develops a thrombotic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity. If the patient is considered to be in hemorrhagic shock and the primary treatment team determines TXA should be administered as part of a massive transfusion protocol or based on local standard of care, emergency unblinding of the treatment arm will be immediately available to the hospital physician. All additional hemostatic agents and blood products will continue to be administered based on the discretion of the individual provider and according to local standard of care and will be recorded. Patients who develop hemorrhagic shock after randomization will continue to receive local standard of care treatment. If the treatment team is treating the patient for hemorrhagic shock and local standard of care includes administration of TXA, emergency unblinding will be required. The hospital physician will contact the ROC DCC's automated unblinding web base or phone system to obtain the field treatment arm if there is a need for rapid emergency unblinding. This will also automatically notify staff at the ROC DCC and the site research personnel via email of the emergency unblinding. The decision to administer additional TXA based on the patient's randomized treatment arm will be based on clinician judgment.

5.2.4 Treatment arms

There will be three treatment arms. The prehospital container for each treatment arm, also known as the study drug kit, will house the blinded study drug vial along with a label for a 250 mL bag of 0.9% sodium chloride for the bolus dose and labels for the IV tubing to flag the patient as enrolled in the TXA for TBI study. An EMS vehicle will carry the study drug kit as a part of their stock supplies. Each kit will be assigned and labeled with a randomization number, which EMS will communicate to the hospital-based research personnel, who then initiates the steps necessary to prepare the hospital infusion for administration.

5.2.5 Drug manufacture and supply

The active pharmaceutical ingredient (API) for the trial drug Tranexamic Acid Injection will be purchased from CUSTOPharm Inc. CUSTOPharm recently contracted with X Gen Pharmaceuticals Inc. for shared ownership of the API license. (see Appendix 4 for TXA Monograph) TXA Injection is a colorless solution packaged in a glass vial and manufactured by Exela Pharma Sciences, LLC in accordance with Good Manufacturing Practices (GMP). Exela will also manufacture the injectable placebo solution (sodium chloride 0.9%) in the same type of glass vial in accordance with GMP. The TXA and placebo vials, being identical in appearance, will be shipped separately in bulk to Almac Clinical Services. Almac will assemble the blinded study vials into custom study kits for the prehospital dose and in multiple mixed vial containers for the in-hospital dose, distribute them to the clinical sites and be responsible for maintaining the Product Specification File until final database lock and unblinding of the trial data.

5.2.6 Blinding

All providers will be blinded to the intervention assignment in a double blind manner. At no point will EMS or hospital providers be able to distinguish the treatment group unless emergency unblinding is required as described in section 5.2.3. Adherence to the treatment protocol will be carefully monitored and protocol deviations will be identified through the data collected or reported to the ROC DCC by study coordinators. The blinding process will involve labeling the prehospital study kits with randomization numbers that will be used as the package identification and labeling the in-hospital dose vials with unique code identifiers that can be matched to the study kit randomization numbers.

5.2.7 Justification for dose selection

The dose selection for the study drug is as follows:

- *Bolus/maintenance arm:* 1 gram IV TXA in 250 mL administered wide open followed by a 1 gram maintenance IV TXA infusion over 8 hours (weight based equivalent: 50 kg person – bolus 20 mg/kg, maintenance 2.5 mg/kg/h; 75 kg person – bolus 13.3 mg/kg, maintenance 1.7 mg/kg/h; 100 kg person – bolus 10 mg/kg, maintenance 1.25 mg/kg/h)
- *Bolus only arm:* 2 grams IV TXA in 250 mL administered wide open followed by a maintenance placebo infusion over 8 hours (weight based equivalent: 50 kg person – bolus 40 mg/kg; 75 kg person – 26.7 mg/kg bolus; 100 kg person – bolus 20 mg/kg)

The doses of TXA to be used in this study are based on studies of TXA in previous trauma trials including the CRASH-2 trial of TXA in trauma patients with significant hemorrhage as well studies performed in surgical patients. Loading doses in these studies have ranged from 2.5 mg/kg to 100 mg/kg with maintenance doses ranging from 0.25 mg/kg/h to 4mg/kg/h over 1-12h.⁴² Studies evaluating different dosing regimens of TXA on bleeding and transfusions have demonstrated no significant difference between the higher and lower doses. In cardiac surgical patients, a 10 mg/kg loading dose of TXA followed by an infusion of 1 mg/kg/h resulted in plasma concentrations sufficient to inhibit fibrinolysis, with no additional hemostatic benefit afforded by higher doses.^{77,78} In the CRASH-2 trial, there was no difference in the rate of vascular occlusive events (1.7% TXA versus 2.0% placebo) and no reported adverse events. In a study of patients with isolated TBI, a single 2 gram dose decreased ICH progression with no adverse events.

The dosing regimens in this proposal were chosen for the following reasons:

1. A fixed dose is most feasible in a prehospital study.
2. A single bolus dose without a maintenance infusion would be preferred for military application.
3. The adjusted per kilo doses for both interventional arms are in the range shown to inhibit fibrinolysis and provide a potential benefit in larger patients (>100 kg), yet have been shown to be safe without adverse effects in smaller patients (<50 kg).

Justification for using standard dosing in subjects with potential renal insufficiency: TXA is eliminated through renal excretion and thus, there is the potential risk of accumulation in patients with renal impairment; however,

the dosing regimen in both interventional arms of this trial involve either a low dose followed by a short course of TXA, or placebo, such that accumulation is expected to be minimal in either arm. For this study, if a history of renal dialysis is known by EMS prior to randomization, the patient will be excluded. If randomization has occurred and the patient's hospital serum creatinine is greater than 2 mg/dL at any time prior to or during the study drug infusion, the study drug infusion will be terminated.

Justification for use in subjects with potential hepatic impairment: Only a very small proportion of TXA is metabolized by the liver, thus there is no need for dose adjustment in hepatic impairment and pharmacodynamic interactions with other drugs should be minimal.

Justification for use in subjects with subclinical seizure activity not evident to EMS or care providers:

In patients undergoing cardiac surgery, high doses of TXA have been associated with seizures;⁷⁹ however, in the CRASH-2 trial there were no reports of serious unexpected adverse events involving seizures in 20,211 trauma patients using similar doses proposed in this trial. In one retrospective review in patients who had undergone pulmonary endarterectomy with hypothermia, an increase in seizure activity compared to aprotinin was observed in patients without structural brain lesions (7 versus 0, $p=0.02$); however, the doses given were significantly higher than the doses to be administered in this trial.⁸⁰ For this study, observed seizure activity or a history of seizure activity will exclude the patient prior to randomization or, if randomization has occurred, cause administration of the study drug dose in the field or hospital to be stopped.

5.3 Baseline Assessment

The baseline data, including demographics, injury mechanism, prehospital and ED hemodynamic variables, time to definitive care, mode of transport, presence of TBI, and fluids and blood products administered within the first 24 hours after injury will be obtained by the research coordinator as soon as feasible.

5.4 Clinical Data Collection

Because patient enrollment will occur at the scene of injury, there is no opportunity for baseline assessment of the patient by the clinical research coordinator; however, the ROC has an established infrastructure to facilitate obtaining all prehospital records including accurate time data from computer aided dispatch reports for all patients. Upon arrival to the hospital, a research coordinator will be available 24/7 at all sites. Direct bedside data collection will begin when the subject arrives in the ED and will continue until the patient receives the initial head CT scan and the hospital infusion is begun or for one hour, whichever occurs later. The time of arrival and time of initial head CT scan will be documented. GCS will be documented at these same time points. Data to be collected during this time period will include all fluid administered including hypertonic saline, all pharmacologic interventions including mannitol, all blood product transfusions, any procoagulant medications administered, history of current use of anticoagulant medications, life-saving interventions including intubation, initial clinical laboratory results, and surgical/neurosurgical procedures.

Data will be collected on a daily basis for the first 28 days of hospitalization or until discharge/death on all subjects who did not choose to discontinue further participation in the trial. Information collected will include demographics, injury scoring data, blood product transfusions, hemostatic medication administration, timing and dosing of DVT prophylaxis, GCS, intracranial pressure, cerebral perfusion pressure, neurosurgical interventions (including intracranial pressure monitor placement, brain tissue oxygen monitor placement, microdialysis catheter placement, ventriculostomy, and decompressive craniotomy/craniectomy), timing of clinically indicated repeat head CT scan (including GCS at the time of repeat CT), other surgical procedures, vital signs, and routine daily lab results. In those institutions where CT is repeated in all patients with intracranial bleeding by protocol, the 2nd CT will be performed 6 hours after the first. Complications recorded will include the following: thromboembolic complications (stroke, DVT, PE, MI) including results of thromboembolic screening procedures (including MRI, duplex ultrasound, PE protocol CT scans, electrocardiograms [EKGs]), results of electroencephalograms (EEG) evaluating seizures, results of transcranial doppler evaluating vasospasm, multiple organ failure (Multiple Organ Dysfunction Score), acute

respiratory distress syndrome (ARDS - based on the Berlin definition), transfusion related ARDS, acute kidney injury, diabetes insipidus, hyper- and hyponatremia, infections, and sepsis. A pre-specified list of clinically indicated available lab results will be recorded and commonly include blood alcohol level, complete blood count (CBC) with platelets, electrolyte panel, coagulation tests (aPTT/ INR), fibrinogen, troponin, lactate, arterial and venous blood gas, and urinalysis. In addition to the information collected daily, the final discharge diagnosis, and discharge destination (home, long-term acute care hospital, skilled facility, death) will be recorded. A discharge GOS-E and DRS as well as a Neurologic Assessment: Symptoms and Signs Present will be obtained at the time the subject is discharged from the hospital. A 6-month GOS-E and DRS as well as a Neurologic Assessment: Symptoms and Signs Present will be obtained at 6 months after injury. (See Appendix 3 GOS, GOSE, DRS and Neurological Assessment: Symptoms and Signs Present)

5.5 Research Laboratory Data Collection

Blood samples will be collected during the first 48 hours after admission from all subjects who have not withdrawn participation in the trial. Blood samples will be collected upon arrival in the ED (time 0) for all enrolled/randomized subjects and at 6, 12, 24, and 48 hours (or discharge from hospital – whichever occurs first). Studies to be performed at these time points include measures of fibrinolytic pathway activity. Kaolin activated TEG will also be performed on citrated blood samples at these time points for functional analysis of coagulation. Available data from these studies will be for research use only and will not be available for clinical decision making. In addition to the studies listed above, blood will be collected and stored at the same time points for inflammatory marker analysis for which additional funding will be sought. Blood will be stored for future testing only related to TBI, intracranial hemorrhage, fibrinolytic pathway mediators and other coagulation factors. The specimens will be stored for future use in a de-identifiable manner such that the patient's identity will not be able to be ascertained. We chose these 5 time points to provide a broad temporal survey of coagulation changes after TBI weighted toward early sampling to fully characterize the early phase of coagulopathy. Later sampling at 24 and 48 hours will allow characterization of the transition from a hypocoagulable to a hypercoagulable state and full examination of the effect of the intervention on coagulation and inflammation after TBI. All attempts will be made to obtain study samples at the pre-specified time intervals and samples at times 0, 6, and 12 hours must be collected within +/- 30 minutes. Sampling at 24 and 48 hours will be collected within +/- 2 hours. In the event that samples cannot be collected in this time frame, documentation regarding the reason will be noted on the data collection forms. Up to 23 ml of blood will be collected in addition to the clinical sampling at each time point. Samples will be collected by the clinical person responsible for implementing physician orders for laboratory testing. The clinical research staff will then be responsible for processing and shipping at each site. All samples drawn for research purposes will be identified by the study number, the site identification number and date/time of collection. No personal identifying information will be included on the samples processed for research purposes. Assays that require immediate processing (TEG and CBC) will be performed at each study site by trained personnel. Other samples will be spun, aliquotted, frozen at -80°C, bar coded, and batch shipped by the clinical research staff to the Trauma Research Institute of Oregon, Oregon Health & Science University. The research laboratory data will be entered into a web based relational database created for the lab measurement component of this trial.

5.6 Image Collection and Processing

To reduce observer variation, we will perform a central review of all CT scans, a process that is considered essential in multicenter trials utilizing imaging studies. Each site will obtain digital images of all head CT scans obtained during the first 28 days of the subject's initial hospitalization in Digital Imaging and Communication in Medicine (DICOM) format, which will be made available electronically by remote access, on a storage device, or via a secured file transfer protocol (FTP) upload site to OHSU CCC within two weeks of a subject's discharge from the enrolling hospital. All MRI scans will be uploaded via the same mechanism to the OHSU image repository. All images will be stored in a de-identified manner. Head CT scans will be reviewed centrally at OHSU under the direction of a neuroradiologist who will be blinded to the treatment group assignment. A technician will be trained to utilize software designed to obtain computerized measurements of ICH volumes. The central neuroradiologist will audit 10% of scans to verify that accurate and consistent measurements are obtained. MRI and CT scans will be maintained in the imaging repository for future

analyses that may include computer-aided lesion analysis and/or regional brain volumetrics.

5.7 Concurrent Care

Prehospital care: there is significant variability in EMS systems resulting in difficulties associated with attempting to standardize care. Prehospital airway, fluid and blood product administration will not be standardized; however, detailed prehospital data will be collected to determine if there are potential differences in important prognostic treatment variables among different study sites. We will encourage the study drug to be administered as soon as possible after life-saving interventions are performed and prior to administration of blood products; however, there may be circumstances where this is not feasible.

In-hospital care: in order to minimize variability in subsequent management of TBI, all sites will have 24 hour neurosurgical capability and will encourage the implementation of management guidelines set forth by the Brain Trauma Foundation that are supported by evidence based medicine.⁹ Additionally, evidence-based guidelines and protocols for critical care management will be encouraged and monitored and will include the following: management of severe TBI, early use of head CT with liberal use of repeat head CT for patients with ICH, massive transfusion protocol, transfusion guidelines for trauma patients, early detection and treatment of myocardial infarction and stroke, mechanical ventilation protocol, sedation/analgesia protocol for mechanical ventilation, early nutritional support protocol, glucose control in the ICU, diagnosis & treatment of ventilator associated pneumonia, adherence to surviving sepsis campaign guidelines, and venous thromboembolism surveillance and prophylaxis protocol for prevention. In cases where a repeat CT is clinically indicated, it will be performed at approximately 6 hours.

5.8 Early Termination of Study Drug

When EMS personnel open the blinded study drug kit, the patient is enrolled and randomized and will be included in the primary statistical analysis if the study drug is connected to the patient's IV access. The study drug will be terminated by EMS or by hospital providers for any of the reasons below.

- Prehospital provider suspects the patient has developed a thrombotic event (MI, ischemic stroke,) or seizure activity OR after hospital arrival the patient develops a thrombotic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity
- The patient requires cardiopulmonary resuscitation (CPR)
- The patient, patient's family member or legally authorized representative (LAR) withdraws from the study
- The patient is discovered to be pregnant
- A serum creatinine > 2.0 mg/dL is obtained
- The patient requires administration of Factor IX Complex concentrates or Anti-inhibitor Coagulant concentrates
- The patient is discharged from the hospital prior to completion of the 8 hour infusion

6. Study Outcome Measures

6.1 Primary Outcome Measure: 6 Month Neurologic Outcome

Two National Institutes of Health (NIH) consensus conferences have addressed clinical trial design for interventions designed to impact outcome from TBI.^{81,82} The first emphasized the importance of assessing long term outcome following brain injury and recommended use of the Glasgow Outcome Score (GOS) for subjects with severe brain injury (GCS ≤ 8) and the DRS for subjects with less severe brain injury (GCS 8-13).⁸¹ A subsequent conference recommended a 6 month follow-up utilizing outcomes that are "measurable, standardized, and relevant to lifestyle."⁸² Specifically they recommended the use of the GOS-E. The rationale for this recommendation is that the GOS-E provides a better distinction between levels of disability, particularly

within the severe disability groups, while the GOS combines a wider range of disability into one category. Furthermore, combining the GOS-E with the DRS increases the ability to detect improvement following TBI.^{83,84,85,86}

Detailed neurocognitive, behavioral, and psychological testing has been advocated for full assessment of neurologic outcome following TBI. This approach requires that the patient return to the trauma center for intensive testing and requires extensive training for those administering the assessments. This approach has not been directly compared against the most widely used measures of GOS-E and DRS. Furthermore, recent experience with this approach in a TBI outcome study demonstrated a 50% rate of refusal by the patients to return for this detailed testing.⁸⁷ Thus, application of these outcome assessments in this trial would exceed available resources, increase the risk of poor inter-rater reliability, and result in inadequate follow-up rates for subsequent analysis.

Extended Glasgow Outcome Score: The GOS was first proposed by Jennet and Bond in 1975.⁸⁸ It is a simple four-point scale based on the degree of patient disability. It has been widely adopted based on its simplicity and high inter-rater reliability.^{89,90,91} An Extended Glasgow Outcome Score (GOS-E) was subsequently developed which further subdivides the categories of severe and moderate disability and good recovery.⁹² Structured telephone interviews have been developed and validated for both the GOS and GOS-E and these questions will be incorporated into our follow-up survey.^{86,92} For each level of function, the baseline function prior to injury is assessed to ensure that the deficit can be attributed to the event. The GOS and GOS-E have been shown to correlate well with several other outcome measurements after TBI including neuropsychological and cognitive testing, the DRS, and measures of perception of health (SF-36).^{85,92,93} The GOS-E will be assessed at discharge and at 6 months after injury. The GOS-E measured at 6 months will be the primary outcome for this trial.

Outcome assessment: Outcome assessment will be performed by telephone survey that includes the key components of the GOS-E and will be administered to patients or their caregivers at the time of discharge for baseline assessment and at 6 months after injury. Attempts will be made to contact the patient directly; however, for patients who are severely disabled, information will be obtained from the primary caregiver. Reliability will be assessed and if the patient is determined to be unreliable, a caregiver will be sought to complete the survey. Previous studies demonstrate that caregiver assessment is a valid means of assessing these outcome parameters.^{92,103,94} Previous follow-up in the TBI population demonstrate variable success in achieving adequate response rates ranging from 73% to 99% follow-up at 6 months.^{95,96,97} The ROC DCC has extensive experience with long-term outcome assessment in both TBI and non-TBI populations. In a large multi-institutional study evaluating prehospital hypertonic saline administration in TBI conducted by the ROC, an 85% response rate was achieved.⁹⁸ We will utilize this model that includes a detailed contact list collected from the patient or family and friends prior to discharge and a log for tracking follow-up attempts by the study coordinators. The Public Access Defibrillator trial used a similar follow-up method and although not a trauma trial, this model resulted in 100% follow-up for the primary endpoint.⁹⁹ In addition, telephone contact at one month post discharge will be initiated to establish a relationship and commitment for the 6 month interview.

6.2 Secondary Outcome Measures

- *Clinical outcomes:* Observed volume (absolute and relative) of ICH progression, proportion of patients who develop observed ICH progression (as defined below), Rotterdam and Marshall CT classification scores, DRS at discharge and 6 months, GOS-E at discharge, 28-day survival, frequency of neurosurgical interventions, and ventilator-free, ICU-free, and hospital-free days.
- *Safety outcomes:* Development of seizures, cerebral ischemic events, MI, DVT, PE
- *Mechanistic outcomes:* Alterations in fibrinolysis based on fibrinolytic pathway mediators and degree of clot lysis based on kaolin activated TEG and defined as LY30 or the per cent lysis that occurs 30 minutes after maximum amplitude (MA) is achieved.

ICH progression is associated with an increased need for neurosurgical intervention and is independently associated with a 5-fold increased mortality in patients with TBI.²¹ If seizures or other adverse outcomes are found in this trial, it will be important to balance the potential benefit in reduction of ICH progression with the risk of an adverse outcome to determine the overall impact of TXA. All clinically indicated head CT scans obtained during the initial hospitalization or within the first 28 days will be assessed for ICH. All cerebral and carotid/vertebrobasilar CT and standard angiograms will be assessed for blunt cerebrovascular injury. Parenchymal, subdural and epidural hemorrhage volumes will be measured and quantified using volumetric software and verified by manual calculations based on the previously validated ABC/2 technique as needed.¹⁰⁰ Ten percent of all scans will be audited by a single neuroradiologist for accuracy. Each case in which a disparity is detected will be discussed with the neuroradiologist resulting in review of additional cases and retraining of the technologist as necessary. Subarachnoid hemorrhage (SAH) will be categorized as ≤ 5 mm or > 5 mm. Intraventricular hemorrhage (IVH) will be visually assessed as present or absent on all scans with progression determined by direct comparison of studies by a neuroradiologist. New focal ischemic lesions will be defined as an area of focal low attenuation in a distribution indicating an arterial ischemic cause rather than a traumatic contusion and will be rated using a validated scale for ischemic stroke.⁶⁰ Mass effect will be defined as sulcal effacement, ventricular effacement, uncal herniation, cistern compression, and midline shift. The following outcome measures will be recorded: the difference in the total hemorrhage volume across scans, determination of significant hemorrhage progression between scans defined as greater than a 33% increase, presence of a new ICH, worsening of SAH grade, worsening IVH or mass effect, and the development of new focal cerebral ischemic lesions. We have chosen to define progression of subdural, epidural and intraparenchymal hemorrhages as an increase of $> 33\%$ over baseline based on the description by Brott et al.¹⁰¹ This number is based on the following: a 33% change in the volume of a sphere corresponds to a 10% increase in diameter, which is considered a clear difference to the naked eye of a physician viewing serial CT scans of a patient with an ICH.¹⁰¹ Thus, this difference can be assessed clinically without using volumetric software applications. Second, previous experience suggests variability in measurement of lesions may occur due to variation in patient positioning and angles of the CT slice images rather than to an actual increase in hemorrhage volume, especially for small hemorrhages. Thus, by using an increase of $> 33\%$, our CT definition of intraparenchymal, subdural, and epidural hemorrhage progression is conservative and is more likely to represent true hemorrhage growth as opposed to variability in CT imaging.¹⁰¹ All MRI scans during the initial hospital stay performed as part of routine clinical care will be uploaded with CT images to the imaging repository for future analyses that may include computer-aided lesion analysis and/or regional brain volumetrics.

The DRS is designed to classify patients based on their degree of function after brain injury. The DRS consists of 8 items that fall into 4 categories: a) arousability, awareness and responsivity, b) cognitive ability for self-care activities, c) dependence on others, and 3) psychosocial adaptability.¹⁰² The DRS has been reported to be more sensitive than the GOS-E for changes in function over the first year following injury.¹⁰³ This may be particularly important for patients with moderate TBI. In this trial we will be enrolling patients with both moderate and severe brain injury. The DRS will be administered to patients or their caregivers at the time of discharge for baseline assessment and at 6 months after injury by telephone survey along with the GOS-E.

Laboratory assessment of coagulation will include fibrinolytic pathway mediators. These mediators are important in the fibrinolytic pathway and will provide insight into the mechanism underlying an observed treatment effect. TEG will be performed at serial time points as a viscoelastic measure of coagulation and fibrinolysis.

7. Sample Size for the Primary Outcome

The primary outcome is favorable neurologic function at 6 months after injury based on the GOS-E > 4 . Good outcome corresponds to either moderate disability or good recovery (GOS-E > 4), while poor outcome corresponds to death, vegetative state, or severe disability (GOS-E ≤ 4). The total sample size in the primary analysis population will be 963 (321 per group). The sample will include randomized patients for whom the

treatment is started (modified intention to treat population). Power computations were based on a comparison of binomial probabilities with assumed variance larger than given by the binomial distribution; the hypothesized additional variance would be contributed by the multiple imputation of outcomes for subjects with missing outcome data. Based on results from the TBI cohort in the ROC hypertonic saline trial,⁹⁸ we assumed that 40% of subjects treated only with placebo would have a poor neurologic outcome (GOSE $\leq$ 4) at 6 months, that 15% of subjects would be missing 6-month outcome data, and that the per-subject additional variance contributed by the multiple imputation of the outcomes was 10^{-6} . Under these assumptions, our sample size will allow for 80% power to detect a 7.1% absolute increase in a favorable GOS-E (> 4) at six months post injury comparing the combined TXA treatment groups to placebo, using a one-sided, level 0.1 test. Similarly, in testing for harm, this sample size will allow for 80% power to detect an absolute decrease of 9.5% in the proportion of patients with a favorable long-term neurologic outcome, using a one-sided, level 0.025 test.

8. Analysis Plan

8.1 Primary Analysis

Primary analysis: The primary analysis will be a modified intention to treat analysis that will include all patients who were randomized and began treatment. Because of the double-blind design of the study, this analysis tests the primary study hypothesis, and with slightly higher power than an analysis of all randomized patients. The primary analysis of this endpoint will use multiple imputation methods to account for missing outcome data, and logistic regression adjusting for site, to compare the combined TXA treatment arms to the placebo arm and estimate the adjusted odds ratio to describe the strength of the association between TXA treatment and favorable GOS-E at 6 months^{104,105,106}. To reduce the chances that we will fail to demonstrate a possible treatment effect in this phase II study, a one-sided hypothesis test at the 0.1 level will be performed to compare the combination of the two treatment groups to the placebo group. To evaluate the possibility that TXA treatment reduces the proportion of patients with good neurologic outcome at six months, a one-sided test at the .025 level will be conducted.

- Safety population: Analysis of treatment safety will be conducted on all patients who had the study drug connected to their IV line. Safety data will be reported on a regular basis to the Resuscitation Outcomes Consortium Data Safety Monitoring Board (ROC DSMB).

8.2 Pre-Specified Secondary Subgroup Analyses

Secondary analyses of the primary endpoint will additionally adjust for baseline prognostic factors including age, gender, prehospital GCS, mechanism of injury, and injury severity. Analyses for secondary outcomes that are binary will be conducted similarly. Additional secondary analyses of the primary endpoint will compare each treatment group separately to placebo, and the two treatment groups to each other. For quantitative secondary outcomes, linear regression analysis with robust standard errors will be used to test for treatment-placebo differences and to estimate the mean outcome difference associated with treatment, after adjustment for site and prognostic variables. Evidence for modification of the effect of treatment in the efficacy population by the presence or absence of additional prognostic factors will be examined using interaction terms in linear or logistic regression models, and estimated treatment differences will be reported separately in subgroups together with the statistical significance of the associated hypothesis tests for interaction. It is recognized that this study is not powered adequately to detect interactions and thus subgroup analyses will be considered exploratory, generating hypotheses for further study.

A priori subgroup analyses will compare outcome between both the combined and individual TXA treatment groups and the placebo group in:

1. Patients who met all inclusion and exclusion criteria
2. Patients who received the full intervention/placebo
3. Patients who receive the prehospital intervention/placebo only
4. Patients with an ICH on initial head CT and repeat head CT performed within 24 hours
5. Patients with blunt vs. penetrating TBI
6. Patients with Head AIS score ≥ 4
7. Patients with Head AIS score <2 (altered mental status likely secondary to intoxication and not significant TBI)
8. Patients requiring emergent craniotomy
9. Patients stratified by no PRBC received versus 1-9 units PRBC received versus ≥ 10 units PRBC received in the first 24 hours
10. Patient who require TXA administration for hemorrhagic shock after being randomized in the study

8.3 Mechanistic Outcomes

Due to the large number of outcomes and potential analyses, results of analyses of these outcomes will be treated as exploratory and will be used to inform the design of future studies that may result in clinical recommendations. These results will be summarized descriptively and will be analyzed using the same methods as for the secondary outcomes in order to give insight into the mechanism(s) underlying the observed treatment effects. Results will be reported using point estimates and the 95% confidence intervals rather than p-values.

8.4 Plan for Missing Data

All possible efforts will be made to avoid missing outcome data. These include collecting detailed contact information from a variety of different sources prior to hospital discharge (address, email, other family members, friends, physicians), contacting the patient/family within one month of discharge to establish a continued relationship, and integrating TXA follow-up with other medical follow-up (e.g. clinic, physical therapy). For the primary analyses, any missing outcomes will most likely be due to study patients withdrawing from participation in post-discharge follow-up or dropping-out. Neurological status at discharge is highly correlated with neurological status at 6 months.¹⁰⁷ Specifically, we anticipate that patients who have a “good outcome” at discharge tend to improve and not get worse and those that have a “poor outcome” tend to remain at the same status or improve. In primary analyses, multiple imputation methods will be used to account for missing outcome data.^{108,109,110} Sensitivity analyses will consider modified worst-case (last observed GOS-E score minus 1) for missing outcomes in all treatment arms, and a modified best-case (last observed GOS-E score plus 1) for missing outcomes in all treatment arms.

8.5 Sequential Monitoring Plan

Because of the fear that selection criteria based only on field data may potentially include subjects who would not be able to benefit from TXA treatment, one formal futility analysis will be conducted based on outcome data from the first 200 subjects in the analysis population and reported to the ROC DSMB, using a Wang-Tsiatis boundary.¹¹¹ The early stopping for futility is described in Table 1. The futility stopping rule would categorize results at the first analysis as futile if the observed crude difference in probabilities of a bad neurologic outcomes (GOSE < 5 at 6 months post injury) corresponded to an absolute increase of 6.8%. As can be seen from the 95% confidence interval, this futility decision would nearly rule out the hypothesized improvement of 7.1%.

Table 1: Protocol Stopping Rule							
		Futility Boundary			Efficacy Boundary		
	N accrued	Z	Crude Diff	Est (95% CI; one-sided P)	Z	Crude Diff	Est (95% CI; one-sided P)
First	200	0.955	.068	-.047 (-.072, .125); P = .82	NA	NA	NA
Second	963	-1.266	-.042	-.048(-.109, .022); P = .10	-1.266	-.042	-.048(-.109, .022); P = .10

Table 2 presents the probability of declaring superiority, futility or inferiority for selected hypothesized values of the true treatment effect. The incorporation of the futility stopping rule affects the power of the study to detect benefit of TXA very little, moving the minimal absolute treatment difference that can be detected with 80% power from -0.070 to -0.071.

Treatment Diff	Pr[superior] (power)	Pr[Futile]	Pr[inferior]
-.071	.80	.20	0
-.05	.59	.41	0
-.03	.35	.64	0
-.02	.25	.75	.01
-.01	.16	.82	.01
0	.10	.88	.02
.01	.06	.90	.05
.02	.03	.89	.09
.05	0	.68	.31
.10	0	.16	.84

8.6 Adverse and Serious Adverse Events

TXA has been in use for decades and the safety profile is well established. Adverse events will be reviewed by the sponsor, which is the ROC DCC, as required by 21 CFR part 312 in addition to other entities delineated. The trial will collect data on adverse events that may be associated with the use of TXA in TBI. These events will be reviewed by an independent medical monitor and reported regularly to the ROC data safety monitoring board (ROC DSMB). The ROC DSMB is a distinct and separate entity from the ROC DCC and functions independently from the sponsor.

While there have been rare cases of thromboembolic events and seizures potentially associated with TXA use, usually at higher doses, there is no evidence that the TXA treatment regimen proposed in this trial is associated with an increased risk of vascular occlusive events or seizures. Nonetheless, data on vascular occlusive events and seizures will be collected as secondary outcomes and will be provided to the independent medical monitor and ROC DSMB for unblinded review as necessary. Emergency unblinding will be immediately available if the primary treatment team determines TXA should be administered based on standard of care (i.e. patients in hemorrhagic shock). While we do not anticipate additional need to perform emergency unblinding, in the event that unblinding is deemed necessary for safety or treatment related decisions during the course of the study, emergency unblinding will be available to the hospital physician.

An adverse event (AE) will be defined as any untoward medical occurrence affecting a trial participant during the course of the trial. A serious adverse event (SAE) will be defined as any medical occurrence that results in death, is life-threatening, requires ICU admission, requires prolongation of existing hospitalization, or results in persistent or significant disability. All members of the patient management team will be instructed as to the

possible adverse events prior to the start of the trial and will be given an emergency contact number to immediately report any suspected adverse event to the site investigators. Any deaths not explained by the injury severity will be reported individually according to regulations regarding serious adverse events. In addition, serious adverse events will be reported in aggregate by blinded treatment group to the medical monitor and ROC DSMB on a regular basis. All adverse events that occur during the study period (after randomization until hospital discharge) will be recorded on the ROC DCC Alert forms found online. All potential adverse events will be reviewed as to the assigned treatment group and further classified by: a) severity (life threatening, serious, non-serious) and b) expected versus unexpected. Expected adverse events, assessed by the site PI, will be monitored by each enrolling site, reported to overseeing agencies as required by federal regulations and local requirements, and reviewed periodically by the ROC DSMB. The ROC DCC will tabulate and report on non-SAEs on a regular basis.

Suspected Unanticipated Serious Adverse Reaction (SUSAR): Unanticipated serious adverse reactions will include potentially related SAEs suspected to be related to study treatment/intervention. The site PI will classify all in-hospital mortality according to underlying and contributing causes most relevant to TBI and other life-saving interventions.

Expected Adverse Events: Common expected adverse events will include: death related to TBI, infectious complications, ventilator assisted pneumonia, acute lung injury, acute respiratory distress syndrome, acute kidney injury, and multiple organ failure. Counts of these will be tabulated and reported to the ROC Data Safety and Monitoring Committee on a regular basis.

SUSAR Reporting Procedure and Databases: In addition to following local reporting procedures, sites will notify the ROC DCC of a SUSAR or possible thrombotic or seizure related death within 3 business days of discovery of the event, and the site will complete an FDA MedWATCH Form within 7 days of notification and within 15 days of notification if the SUSAR is not life threatening. For a SUSAR, the ROC DCC will notify the medical monitor, ROC DSMB, appropriate regulatory agencies (FDA, Health Canada), ROC DCC IRB, site IRBs/Research Ethics Boards (REB), and the Department of Defense (DoD) promptly.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study must be promptly reported by phone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000-us.

Infusion Discontinuation Rules: Any thromboembolic event (MI, PE, ischemic stroke, or symptomatic DVT) or seizure activity will prompt cessation of the infusion and a medical safety review. Further detail regarding specific clinical indications for stopping the study drug early will be provided in the manual of operations.

8.7 Other Adverse Events

Due to the short duration of the study and the six-month time period between enrollment and primary outcome measurement, there will be no formal interim analysis, however, regular ROC DSMB meetings will be held every six months. All other adverse events will be reported to an independent medical monitor and chair of the ROC DSMB, reviewed at regular ROC DSMB meetings and included in a safety report to the FDA. All adverse events and protocol violations will be reviewed. The Chair of the ROC DSMB can convene additional meetings as necessary.

8.8 Roles and Responsibilities of the Medical Monitor

An independent medical monitor will review all unexpected problems involving risk to subjects or others, SAEs and all deaths related to TBI and provide an unbiased written report of the events. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of an SAE or TBI-related death, comment on the relationship to participation in the trial. Because a moderate number of deaths (approximately 15% based on Trauma Epistery Registry data for patients with $GCS \leq 12$)⁷ are expected due to the presence of moderate and severe TBI in the subjects enrolled prior to the intervention, individual reports to the ROC DSMB will be aggregated and reported on a timely schedule acceptable to the ROC DSMB. If the death is considered unexpected and is either suspected or probably due to treatment, this event will be promptly reported to the medical monitor and the ROC DSMB. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator. Reports for serious adverse events determined by either the investigator or medical monitor to be possibly or definitely related to participation must be promptly reported per FDA, DoD and/or Health Canada guidelines.

Dr. Ernest Moore is the independent medical monitor for this study. He has committed to comply with the following statements:

The monitor:

- [X] Is independent of the research team.
- [X] Possesses sufficient educational and professional experience to serve as a subject advocate.
- [X] Will promptly report discrepancies or problems to the IRB.
- [X] Has the authority to stop the research in progress, remove individual subjects from the research, and take whatever steps are necessary to protect the safety and well-being of the subjects until the IRB can assess the monitor's report.

8.9 Data Entry

The ROC DCC uses a sophisticated secure data entry website with a separate home page for each protocol that allows case initiation and look up, access to references such as web entry instructions, form worksheets, manual of operations, a form completion matrix, training resources, a request system used as a formal channel of communication between the sites and the ROC DCC and an on-line inventory management system. To permit managing thousands of subjects in all its studies and registries, the website has an interactive episode list that allows filtering, sorting, and accessing cases and specific forms of interest. The data entry website employs many kinds of data entry quality controls, including field checks, within-form consistency checks, across-form consistency checks, and across protocol-case consistency checks. Some checks cannot be bypassed, some can be overridden with an optional explanation, and some can be overridden only after consulting with the ROC DCC project managers. The system provides live reporting on these checks to enable the ROC DCC to detect large and/or subtle patterns of data entry error. A flexible monitoring system allows for email notification to the ROC DCC and the addition of an alert form to the episode when data entered could be considered a protocol violation or deviation. All actions on the data entry website, such as modification of forms, are logged with the user and a timestamp to provide a complete history of any data point in the database. This facilitates resolution of any question arising from incidental and routine review of the data.

8.10 Database Management

Data collection and analysis will be organized into 3 tiers. First, data will be collected via the web as described above into the data collection relational database; most quality control measures will be employed at this stage to ensure data entry quality. Data will be pulled from this database and formed into a 2nd transitional database. At this stage, additional data that are not directly the result of data entry will be added, such as calculated variables. Data can then be exported for analysis in most statistical software packages.

Computer servers are housed either on site at the ROC DCC or are managed by University of Washington Information Technology (UW-IT) at one of the UW data centers. Daily backups are made of the most important data: the web portal, relational database, the shared file server, and key files from personal computers. Tape backups of the same data are made and taken offsite on a weekly rotation, and scheduled less frequently, a tape backup is kept offsite in accordance with current applicable UW records retention policies.

9. Human Subjects Research

9.1 Potential risks

The patients in this study will be randomized to 1 gram TXA bolus with 1 gram TXA 8-hour maintenance infusion versus 2 gram TXA bolus with placebo 8-hour maintenance infusion versus placebo bolus and 8-hour maintenance infusion. TXA has been associated with seizures and increased risk of thrombotic events. These potentially negative outcomes form the basis for the secondary outcome measures. Children estimated to be less than 15 years of age, women who are known to be pregnant, and prisoners will be excluded from this trial. The ROC DCC will advise the site IRB/REB's and clinical investigators that review and approval of the protocol must satisfy the applicable sections of 21 CFR 50 Subpart D, Additional Safeguards for Children in Clinical Investigations.

In accordance with FDA regulations, we will develop an adverse event reporting system to identify and treat any potential adverse events. We intend to closely monitor the clinical course of all patients enrolled in this trial to identify any expected or unexpected adverse events. Data regarding adverse events will be collected in both a structured (standard form) and open (describing any difficulties encountered) format. Expedited serious adverse events will be reported by the ROC DCC to the Medical Monitor, FDA, ROC DSMB, DoD, ROC IRB and site IRB/REB's in the timelines as required by 21 CFR 312.32. In addition, aggregate reports regarding other safety endpoints will be reviewed by the ROC DSMB at their meetings.

9.2 Potential Benefits to Placebo Arm

Due to the Hawthorne effect, patients in both arms of the study may anticipate improved outcomes due to the additional training and focus by both prehospital and hospital personnel. The benefit to society involves a critical evaluation of antifibrinolytic therapy in a patient population that is likely to benefit from the intervention. Results from this study could form the basis for a significant improvement in the management of TBI.

9.3 Protection Against Risks

9.3.1 Protection of Human Subjects and Consent

This study qualifies for the "Exception from informed consent required for emergency research" outlined in FDA regulation 21CFR50.24.

1. Subjects are in a life threatening situation and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the particular interventions
2. Obtaining informed consent is not feasible because the subject cannot give reasonable consent due to medical condition, intervention must be given before consent can be obtained from a LAR, and cannot prospectively select subject
3. There is prospect of direct benefit to subject because they are in a life-threatening situation requiring intervention, risks associated with this study are reasonable compared to standard of care therapy
4. The research could not be practically be carried out without the waiver
5. Diligent attempts will be made to contact the LAR or family member for them to object to subject's continued study participation within the protocol-defined therapeutic window.
6. IRB has reviewed and approved the informed consent procedures and documents to be used with the subjects or LAR for this study

7. Additional protection of rights will be provided which will include: community consultation and public notification, an established independent data safety monitoring committee, and efforts will be made to obtain informed consent from family members if the LAR is not available

A detailed explanation of each criterion stipulated in the regulations for this exception and how our trial design applies to these criteria is outlined in Appendix1.

This study qualifies for the “Exception from informed consent required for emergency research” outlined in FDA regulation 21CFR50.24. Based on previous data, TXA is anticipated to be most effective if administered immediately following injury. In this uncontrolled setting the patient has an altered mental status secondary to brain injury, which can cause confusion and loss of consciousness. As a result, the patient is unable to provide consent for study enrollment. Legal next-of-kin are often not immediately available at the injury scene, nor is it typically feasible for the prehospital or ED providers to explain the study and receive consent while caring for the critically injured patient. Taken together, these issues provide sufficient support for an exception from informed consent in order to evaluate an intervention that may have significant outcome benefits to this patient population. For the rare scenario where family members and/or next of kin are available at the injury scene and an opportunity for consenting them presents itself, a short script providing information regarding the study will be made available to the family members/next of kin such that they have an opportunity to withdraw consent for the patient’s participation in the study. Once the subject arrives in the hospital the site principal investigator or a designated member of the research team will make frequent attempts as soon as feasible, per local IRB/REB requirements, to contact a LAR and/or family member to obtain consent for continued participation and provide an opportunity to withdraw from participation in the study. A verbal withdrawal will be considered binding. Attempts to contact will include direct contact, telephone contact and written contact or any other contact options as approved by local IRB/REB policy. An assessment will be done at the time of approaching the LAR/subject for consent to assure the LAR and/or subject is competent to make a sound decision regarding the consent process. In the event that the subject does not survive following the traumatic injury, their information will be included in the data analysis. Written notification may be sent to the deceased’s family regarding their participation in the study, per local IRB/REB policy. Due to the severity of the injuries incurred, it is difficult to specify the time frame involved with obtaining the consent, however multiple attempts will be made to obtain consent prior to completion of the study requested blood tests (72 hours after hospital arrival).

The requirements for community consultation/public disclosure will be determined by each institution’s local IRB/REB. All sites have experience conducting random telephone surveys as well as developing and completing community consultation and public disclosure processes. The ability and method of opting out of the study will be determined by local IRBs/REBs. Community consultation will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB/REB may suggest targeting specific groups such as teenagers. The community consultation plan for each study site will be individualized to fit the IRB/REB requirements. The ROC sites have considerable experience conducting community consultation and have published these experiences. A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys, and community meetings. Most sites provide an “opt out” process determined by their local IRB/REB. This process allows members of the community to identify themselves if they choose not to be involved in the study. The associated “opt out” identifier is often in the form of bracelets or identification card. Prehospital personnel will be trained to check for these “opt out” identifiers prior to enrolling any patient. Public disclosures will be performed both prior to study enrollment and at the completion of the study in the form of multimedia press releases organized by the ROC and by local sites. Local sites may decide to target notification to specific community groups such as teenagers, biking clubs, motorcycle clubs, etc. at the direction of the local IRB/REB. These will include plans for the study, including potential risks and benefits, equipoise and a summary of the results of the study upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the study. Information regarding the study will also be available on the ROC website.

9.3.2 Vulnerable populations

Across the US and Canada the laws defining the adult population as related to consent differ from an age of 15 years at the youngest to 21 years at the oldest. In order to consider this wide variability, all consent related procedures, forms, and notification documents will be approved by the participating sites local IRBs or Canadian Research Ethics Boards (REBs) prior to the onset of the study.

This study may include subjects age 15 to 20. Subjects sixteen years of age and older are considered as adult trauma subjects in a large percent of the trauma centers. Sixteen and seventeen year olds are able to drive in most states and are at high risk for motor vehicle accidents resulting in blunt or penetrating injuries. Excluding this age group would significantly decrease our efforts to randomize 963 subjects in a one year period of time. Additionally, it is difficult to differentiate a 16 or 17 year old from one who is 21 or older at the time care is initiated in the prehospital setting until positive identification can be obtained. Children below the age of 15 or 50 kg body weight will be excluded from this trial. Children's intravascular volume is different than the adult's, requiring adjustments to the standard adult treatment protocols. In addition, this study will be conducted at Level I trauma centers which may or may not have affiliated pediatric programs.

Known or suspect pregnant women will be excluded from this study due to the lack of controlled studies in this population.

Suspected or known prisoners (defined as any individual involuntarily confined or detained in a penal institution or any individual in police custody who requires a police escort at all times) are excluded. It is possible that subjects may be enrolled who are under observation as suspects and become prisoners at some point during their hospitalization or following discharge. Office of Human Research Protections (OHRP) approval of an IRB/REB prisoner certification allows the research procedures and data collection to continue for any patient who becomes a prisoner after enrollment. As with any other enrolled subject, consenting and/or notifying the patient, family, and/or LAR with the option to withdraw is required. Participating site IRB/REB's will seek prisoner certification approval from OHRP.

A Certificate of Confidentiality will be obtained from the National Institutes of Health (NIH) to protect the privacy of subjects by protecting identifiable research information from forced disclosure. The Certificate of Confidentiality will allow the investigators and other research associates who have access to research records to refuse to disclose identifying information on subjects in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. For example, during the 6-month GOSE interview, information that if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, the Certificate of Confidentiality will help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants.

9.4 Proposal Timeline

The following is the proposed timeline for this trial: Submit protocol to ROC Protocol Review Committee (September 2013), submit to ROC DSMB (October 2013), submit to FDA for IND (September 2013), obtain ROC DSMB final approval (November 2013), obtain FDA IND approval (January 2014), begin web data entry design and programming (January 2014), begin site IRB/REB submission (Jan 2014), begin community consultation (Mar 2014), start public notification (May 2014), final IRB approvals and web data entry completed (May 2014), DoD Human Research Protection Office (HRPO) approval (May 2014), first site enrolls (June 2014), last site begins enrollment (Sept 2014), last patient enrolled (June 2015), final data cleaning and data analysis (Dec 2015), final analysis (Feb 2016), primary manuscript submitted (May 2016).

9.5 Public Purpose

TXA has been shown to safely reduce the risk of death due to bleeding in thousands of injured patients across the world. The absolute benefit has ranged from 1.5% in a broad population of injured patients, to 6.5% in injured warfighters receiving a blood transfusion, to 13.7% in those requiring a massive transfusion. Thus, in the most severely injured patients the number of people that need to be treated to save one life is only 7. TXA has not been well studied in TBI. In the largest study of patients with TBI and ICH, TXA use was associated with a decrease in the volume of ICH progression by 27%. This is extremely important because progression of ICH is independently associated with a 5-fold increase in mortality. Since TBI is the leading cause of death and disability due to trauma and is the number one cause of death in young people, if TXA is shown to improve outcome in patients with TBI, it could be one of the most important advances in the treatment of TBI to date.

9.6 Military Significance

TBI is a major cause of death and disability on the battlefield. Veterans who have suffered TBI have life-long functional limitations, as well as a high incidence of post-traumatic stress disorder and suicide.¹¹² Efforts to treat TBI in the field include avoiding hypotension and secondary brain injury. Current Tactical Combat Casualty Care (TCCC) guidelines do not directly address the management of casualties with TBI except for providing an adequate airway, maintaining the arterial oxygen saturation > 90%, and avoiding shock.¹¹³ There is currently no effective therapy that offers the potential to improve the return to duty rate and decrease death and disability among warfighters. The MATTERS trial showed improved survival in a military population despite the fact that patients who received TXA were more severely injured and more coagulopathic.⁵¹ TXA has tremendous potential to limit ICH progression, reduce surrounding brain edema, minimize cellular injury and improve long-term neurological outcome after TBI. TCCC guidelines recommend a 1 gram bolus of TXA followed by a 1 gram infusion over 8 hours for hemorrhagic shock or those at risk for major bleeding. The current proposal has the potential to significantly change these recommendations. First, a positive trial would potentially broaden the field indications for TXA to casualties with TBI. Second, an improved understanding of the safety profile of TXA use in TBI will allow TXA to be given safely to warfighters with both hemorrhagic shock and head injury. Finally, we propose studying a single 2 gram dose of TXA delivered in a manner that would be far more feasible to administer in austere or hostile conditions than the current method that requires a continuous infusion over 8 hours. The results of this study will be highly relevant to the military and could provide the foundation for expanding military guidelines for treatment of injured warfighters with TBI.

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Appendix 1: Exception from Consent for Emergency Research

We have outlined below each criteria stipulated in the regulations for this exception and how our study design applies to these criteria.

Sec. 50.24 Exception from informed consent requirements for emergency research

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized investigations, is necessary to determine the safety and effectiveness of particular interventions.

The proposed trial is a randomized, controlled trial of Prehospital Tranexamic Acid Use for Traumatic Brain Injury. The randomized drug regimen of 1 gram TXA followed by 1 gram 8 hour drip, 2 gram TXA followed by 8 hour placebo drip, or placebo initial dose, and placebo 8 hour drip to be initiated as soon as feasible to victims of blunt or penetrating moderate to severe head injury (GCS ≤ 12) and no initial hypotension (SBP > 90 mmHg). These patients are in an immediate life threatening situation with mortality of $> 25\%$ with 1/3 of patients surviving to experience mild to moderate neurologic deficit. Standard of care for prehospital management of these patients includes the rapid infusion of crystalloid solutions without any pharmacological interventions to control hemorrhage or secondary inflammatory injury.

As reviewed in this proposal the extent of brain damage experienced by patients with TBI is determined by the extent of the primary injury as well as of secondary injury consisting of coagulopathy and inflammation. TXA has been shown to prevent hyperfibrinolysis which may limit progression of ICH and reduce cerebral edema through its action on plasminogen. TXA is an established drug for hemophilia to reduce or prevent hemorrhage and to reduce the need for replacement therapy during tooth extraction. Its profile in those indications and doses is known. TXA has recently been the subject of a large multicenter trial targeting its use to control hemorrhage in patients suffering from traumatic injuries including a subset of TBI patients. Although the safety profile of these patients was not well captured, there did not appear to be a large number of associated adverse events if TXA was given less than 3 hours after injury. In a smaller trial TXA was associated with a significant reduction in the rate of re-bleeding. Our trial will administer TXA in the prehospital setting as soon as feasible after TBI and will capture more thoroughly the safety data on this population through our rigorous trial administration and data capture. No new pharmacological therapy has been implemented for routine use in acute TBI in over 30 years.¹² Mortality in patients with severe TBI is greater than 25%¹³ yet one third of patients still survive with minimal to moderate neurologic deficits. Given this wide variability in neurological recovery, an effective treatment for TBI has the potential to significantly impact neurologic outcomes.

(2) Obtaining informed consent is not feasible because:

- i. The subjects will not be able to give their informed consent as a result of their medical condition;**
- ii. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and**
- iii. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.**

(i, ii & iii) In order to perform this trial, the initial dose of the randomized intervention will be administered within a short time of EMS arrival at the injury scene; estimated to be 5-10 minutes. The patient will often have altered mental status as a result of the injury or require intubation. The patient is often unable to provide consent for study enrollment as a result of their injuries. The legal next-of-kin are often not immediately available in the prehospital setting or when the patient arrives to the ED. Because this trial involves traumatic brain injury which is unpredictable, there is no way to prospectively identify individuals who are likely to become eligible for this trial. We will inform the family member or LAR at the earliest feasible opportunity of the subject's inclusion in the clinical investigation, the details of the investigation, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. Such notification is not usually feasible before or at the actual time of treatment and may be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible unless otherwise directed by an IRB/REB.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

- i. Subjects are facing a life-threatening situation that necessitates intervention;**
- ii. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and**
- iii. Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.**

(i) As defined, these patients with traumatic brain injury are facing a life threatening situation which requires immediate intervention.

(ii) Previous trials studying TXA have been conducted in the trauma population and suggest a survival advantage overall and significant direct benefit to patients with TBI if given as soon as possible and within the first 3 hours of injury.

(iii) There are currently no available medications that have been shown to improve outcome for patients with moderate and severe TBI. There have been two randomized controlled trials examining the use of TXA in patients with moderate and severe TBI. One of these trials used the 1 gram bolus followed by 1 gram infusion dose being utilized in one of the arms of this trial.¹ The other trial utilized the 2 gram bolus dose being used in the second treatment arm of this trial.² Both trials demonstrated statistical trends toward decreased progression of intracranial hemorrhage (ICH) and decreased mortality in patients receiving TXA compared to placebo. Furthermore, no increase in thromboembolic or other complication was observed.

(4) The clinical investigation could not practicably be carried out without waiver.

This trial could not be conducted without waiver of consent due to the need to administer the study medication as part of the initial resuscitation of the patient.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

The initial resuscitation time period for this trial begins at the time the paramedics arrive at the patient in the injury scene. Resuscitation and intervention protocols are often initiated within the first 5-10 minutes of EMS arrival. Due to the nature of the injury and the intensity of the resuscitation efforts, it is not often feasible to obtain consent prior to the resuscitation protocol being initiated and prior to randomization into the study. The legal next of kin are often not immediately available when the EMS arrives at the patient's side. However, a script will be provided when feasible in the prehospital setting to inform patients, their legal representative, or family member of the study and allow an opportunity for verbal objection to study enrollment or to withdraw from further participation in accordance with FDA regulations under 21 CFR 50.24. But it is acknowledged that the acute circumstances may only rarely if ever afford such opportunity.

Once the patient arrives in the emergency department (ED) resuscitation continues. The family is not usually present during this time. We will, however, make a reasonable attempt to contact a LAR for each subject at the earliest feasible opportunity to obtain consent rather than proceeding without consent. The LAR or family will be informed of the subject's inclusion in the clinical trial, the details of the trial, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefit to which the subject is otherwise entitled. Such notification is not usually feasible before or at the time of treatment and must be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by a local IRB/REB).

Informed consent will be obtained from patients or their LAR of the study when feasible. In addition, due to the continuation of the intervention into the hospital, repeated attempts will be made to contact that patient or LAR at the earliest feasible opportunity after hospital arrival to notify them of study participation and seek consent for ongoing participation. Efforts to contact LARs will be tracked and reported to the local IRB. Attempts will continue to obtain consent from the LAR and/or patient throughout the hospitalization.

Attempts to contact will include direct contact, telephone contact and written contact of any other contact options as approved by local IRB policy. An assessment will be done at the time of approaching the LAR/subject for consent to assure the LAR and/or subject is competent to make a sound decision regarding the consent process.

When approached for notification of study participation following enrollment, the patient or their LAR will have the option of withdrawing from the study. During the notification process, the details of the trial will be reviewed along with potential risks and benefits, the endpoints of interest and the process by which these endpoints are evaluated. When notified of trial enrollment, the patient or their legal representative will be given the opportunity to withdraw from further data and sample collection. If the patient or LAR withdraws, all further data collection and blood sampling will cease. A verbal withdrawal of the subject's further participation in the study will be considered binding. Data collected prior to the point of withdrawal will be reviewed for study purposes. All research laboratory samples collected up to the point of withdrawal will be obtained and analyzed. In this circumstance, we will be limited to a description of baseline data and data collected up to the point of patient withdrawal to ensure that subjects who withdraw are comparable among the groups. Our previous experience suggests that refusals of this nature are rare. It will be up to local IRBs/REBs to determine if and when a written consent form is required for continued participation.

As this is an emergency research study we will be seeking an emergency waiver of consent. We will contact the LAR for continued trial participation, at the earliest feasible time for the LAR to provide informed consent. All study procedures already performed and yet to be completed will be explained, consent for continued participation will be requested as well as consent for follow-up after hospital discharge. If the subject becomes competent to provide consent during their admission, he/she will be approached by the research coordinator for approval for all study procedures including the 6 month follow-up interviews.

Taken together with the lack of current satisfactory treatment, the life-threatening nature of these trauma types, and the prospect of benefit to participants, these factors provide sufficient support for an emergency exception from informed consent in order to evaluate an intervention that may have significant outcome benefits to this patient population.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

All procedures and consent forms will be approved by the regional study site (Institutional Review Boards (IRBs) or Canadian Research Ethics Boards,(REBs) prior to the onset of the trial.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

i. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

Public notification and community consultation in accordance with local IRB and Canadian REB policies will be undertaken prior to IRB/REB approval. Because the population eligible for enrollment includes all citizens in the study regions, it will not be possible to target specific individuals although the local IRB/REB may recommend targeting specific groups. The community consultation plan for each trial site will be individualized to fit the local IRB/REB requirements. The participating sites have considerable experience conducting community consultation. A variety of methods are employed including consultation with community leaders and targeted community groups, random telephone surveys, and community meetings. Most sites provide an opt-out process to individuals who do not want to be enrolled. The opt-out process allows all members of the community to identify themselves if they choose to not be involved with the study. For this study, the opt-out identifier (i.e., colored bracelet or identification card) will be determined by the local IRB and will be made available through the community consultation programs. The identifier can be given to the individuals at time of meeting or mailed out to the individuals requesting the opt-out process. Prehospital personnel will be trained to check for these patients prior to randomization.

ii. Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(ii) Our suggested approach to public disclosure/community consultation will follow techniques previously approved by local IRBs/REBs and employed at individual centers, such as random-digit dialing, open-forums, public announcements via newspaper or radio, and other locally approved methods of contact with the public. Visual aids, such as power point, flyers or posters can be used in the presentations, and all material will be in lay terminology. Each communication will include information as to the purpose of the trial, the consent process, the risk and benefits to the community/patient, and the time commitment required. As each community is unique and may require specific or special needs, the local IRBs/REBs will approve the methods for their community and ensure that community consultation practices are both appropriate and complete before consent is given to begin the trial.

iii. Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iii) Public disclosures will be performed both prior to trial enrollment (with opportunity and a mechanism for the community to contact the investigators with their response) and at the completion of the trial in the form of multimedia press releases organized by the ROC and by local sites at the direction of the IRB/REB. These will include plans for the trial, including potential risks and benefits, and a summary of the results of the trial upon completion. In the event that the press releases are not widely circulated, advertisements will also be placed in local papers describing the trial. Information regarding the trial will also be available on the ROC website.

iv. Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;

(iv) An independent data safety monitoring board will exercise oversight of the study.-and

v. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation.

(v) We expect that the majority of subjects who meet the enrollment criteria will either be unconscious or have an altered mental status secondary to acute blood loss, traumatic brain injury or intoxicating substances, and thus will not be in a position to provide informed consent in the Prehospital or ED setting. Accordingly, it may not be feasible to attempt to obtain informed consent during the therapeutic window. We will inform the family member or LAR at the earliest feasible opportunity of the subject's inclusion in the clinical trial, the details of the trial, other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. (See more details in item 5 above.) Such notification is not usually feasible before or at the actual time of treatment and must be deferred until after resuscitation efforts have been completed. Such notification will be in person wherever possible and as soon as feasible (unless otherwise directed by a local IRB). A local log will be kept to document the attempts made to contact the LAR/family member.

vi. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(v &vi) A script will be provided to explain the study to patients, their legally authorized representatives, or family members prior to study enrollment whenever feasible. In addition, patients, their legally authorized representative, or family member will be contacted as soon as feasible to be notified of study participation, give permission for 6 month follow up calls and be allowed an opportunity to withdraw from the study. For those who withdraw no further data will be collected beyond the withdrawal date except for vital status at hospital discharge. These efforts will be documented and reported to the IRB/REB per local requirements.

(8) References

¹ CRASH-2 Collaborators. Effect of tranexamic acid in traumatic brain injury: a nested randomized, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). *BMJ*. 2011; 343:d3795.

² Yutthakasemsunt S, Kittiwattanagul W, Piyavechvirat P et al. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emergency Medicine*. 2013; 13:20

Appendix 2: Suggested Templates for Consent and Notification Forms

Sample Prehospital TXA Use for TBI Emergency Provider Script for Verbal Exception from Informed Consent Participation

[\[Insert name of institution\]](#)

Study Information Script

Prehospital Tranexamic Acid Use for Traumatic Brain Injury

Prehospital Study Information and Opportunity for Verbal Objection to Enrollment

Instructions:

While at the scene when the emergency medical system (EMS) provider determines the injured person has met the study inclusion and exclusion criteria, the following information may be provided as feasible to the conscious and alert patient, legally authorized representative, and/or family member of the patient who has experienced injury from trauma.

The purpose of the study information script is to attempt to provide an opportunity for verbal objection to study enrollment or to offer the opportunity to decline further participation, if already enrolled, only if the situation is both safe and does not adversely affect patient care and/or transport. The acute circumstances should only rarely, if ever, afford such opportunities.

EMS providers will be trained to attempt notification only in situations when feasible to conscious or alert patient, legal representative or family member.

Script:

1. You (or your loved one) appear to be at risk for brain injury and needs treatment to protect the brain from further injury.
2. I want to let you know that we [\[Local emergency medical service\]](#) are conducting a research study that tests the use of a medication to treat brain injury which is commonly used to control bleeding in hopes of saving more lives.
3. Treatment needs to be done quickly, but we want to give you the option of not being enrolled in the study.
4. If you say no we will treat you (or your loved one) according to our standard protocols. Someone will give you more information when we reach the hospital.

Sample - Prehospital TXA Use for TBI Consent/Notification

[\[Insert name of institution\]](#)

Continued Participation Consent/Notification Form

Prehospital Tranexamic Acid Use for Traumatic Brain Injury

Investigators

[\[List name, title and phone numbers\]](#)

24 hours Emergency Telephone Number: [\[emergency phone number\]](#)

Ask for the [\[PreHospital Research Coordinator\]](#) on call

Researcher's Statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to continue to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to continue to be in the study or not. This process is called "informed consent". We will give you a copy of this for your records.

If you are unable to provide written informed consent, a legally authorized representative (LAR) may consent on your behalf to continue to take part in this study.

Purpose of the Study

Bodily injury from a physical force to the head can damage brain cells and blood vessels, which may cause bleeding in the head. Emergency treatment is given to protect the brain cells that were not injured from damage caused by interruptions in the blood supply.

Tranexamic Acid (TXA) is a medication commonly given to control bleeding. This study compares the effectiveness of two methods used for giving TXA as early as possible following head injury. The two parts of this study are:

1. How effective is the medication during the early time period after the injury?
2. How effective is the medication 6 months after injury?

When medics determined your head was injured, a decision was quickly made to enroll you in this study. Special permission has been granted by our review board here, the [\[name of IRB/REB\]](#) (IRB/REB), the Food and Drug Administration (FDA), Health Canada and the U.S. Army Medical Research and Materiel Command (USAMRMC) Human Research Protection Office (HRPO) to enroll subjects in this study without their prior consent due to the emergency nature of their injury. The IRB, FDA, Health Canada and HRPO oversee the safety of subjects in medical research.

This study will enroll 963 patients at 10 sites across the United States and Canada. The study will enroll approximately [\[xx\]](#) patients here in [\[city/county\]](#). One third of the patients will receive the traditional method of receiving TXA, one third will receive a modified method, and one third will receive only a salt water solution with no active medication.

Study Procedures

If you (or patient's LAR) agree to continue in this study, your medical and surgical care will not be changed. You were enrolled in this study by the medics who first cared for you and brought you to the hospital. Because the situation was potentially life-threatening, medics provided emergency life support interventions for airway, breathing and circulation. Afterward they observed physical symptoms of head injury that made you eligible for this study. Medics performed all clinically necessary treatments and procedures considered to be standard of care. In addition, medics opened a package that contained either a vial of 1 gram TXA, a vial of 2 grams TXA or a vial of salt water, which they mixed into a bag of intravenous fluid. This bag of fluid was given to you immediately through a tube connected to a catheter inserted into a vein.

The package and vial were designed so that the exact contents of the vial could not be known by the medics. The packages were organized in a randomly assigned order and labeled with numbers linked to a list of the vial content that is not available to the medic. This method ensured that the vial the medics used for you was the result of chance, like flipping a coin.

When you arrived at the hospital, the prehospital study drug kit number was given to the study research staff. The research staff used the kit number to access the list that links the number to the vial needed to administer the in-hospital infusion. The direct care providers do not have access to information about the content of the vial unless the doctor determines it is necessary. In this manner, the pharmacist or nurse will mix the blinded vial containing either 1 gram TXA or salt water in a second bag of intravenous fluid. This second bag is given slowly over 8 hours. Once the second bag of study drug is finished, you do not receive another. This study treatment is performed in addition to all clinically necessary treatments and procedures considered to be standard of care.

Blood samples for research testing (about 2 tablespoons each) are collected on arrival to the hospital and at 6, 12, 24, and 48 hours, if you are still in the hospital at that time. The special blood samples for this study will be shipped to the Trauma Research Institute of Oregon, Oregon Health & Science University and used to look at:

1. How your body reacted to the injury
2. How your blood is clotting (or clumping together)
3. How your body has reacted to the fluids and treatments you received
4. Tests in the future not yet known at this time (*No genetic testing will be done for this study. We will ask for your consent to perform genetic testing at another time for a separate study.*)

Blood will be stored for future testing related to head injury and blood clotting factors. The specimens will be stored for future use in a de-identifiable manner such that your (the patient's) identity will not be able to be known.

Your hospital records will be reviewed. Information will be collected such as procedures, tests, complications and vital signs. Head CT and MRI scans will also be sent via a secure electronic file transfer protocol to the Trauma Research Institute of Oregon, Oregon Health & Science University and maintained in an imaging repository for future analyses. These scans will be stored in a de-identifiable manner such that your (the patient's) identity will not be able to be known.

If you were transferred to another hospital setting, we will ask for your permission to contact that facility to follow up on your progress. You will need to sign an additional HIPAA form to allow us permission to contact the other hospital and get your medical information.

Immediately prior to being discharged from the hospital, research staff will ask you to answer questions about your ability to perform regular daily activities. With your permission, we will also contact you by phone one month after you are discharged to home. At that time we will confirm your contact information and remind you about the final phone call at 6 months following your injury. This final phone call will take approximately 30 minutes. We will ask you to compare your ability to perform regular daily activities before your injury and after your injury. For example we will ask you about eating, drinking and personal hygiene activities, like washing your face and brushing your teeth. Your care giver or family member may respond to these questions for you. You have the right to refuse to answer any of the questions.

Risks, Stress, or Discomfort

Participation in this study may involve some added risks or discomforts, although TXA is now being used in many hospitals and many countries safely to treat bleeding problems.

Adverse events might include:

1. Too much TXA is given - if the amount given is too large you may experience eyesight disturbances, nausea, vomiting, seizures. These are very rare and the dose given for this trial have not been known to cause those problems.
2. TXA given too quickly - If the amount of medication is given too quickly you may experience low blood **pressure which may cause decreased blood flow to your head. When you have a head injury**

this may be associated with complications and a possible risk of death. The TXA in this study is diluted and given over a period of time to decrease the chances of this happening.

3. Any dose – TXA increase the risk of blood clots to vital organs. If this occurs, the medication will be stopped immediately.
4. Skin irritation at the site of infusion or a rash due to a minor allergic reaction with no effects on your blood pressure or heart rate.
5. You may have an allergic reaction to the TXA (including severe immediate reactions) as is possible with any drug.
6. Whenever personal information is collected, there is always the potential that someone who is not authorized by this consent form may see your information. However, steps will be taken to minimize this risk.

If you suffer any injury as a result of this study, please understand that nothing has been arranged to provide free treatment at [\[insert site name\]](#) or any other type of payment. However, all facilities, emergency treatment and professional services will be available for your use just as they are to the community in general.

If you have had any injury, bad effect, or any other unusual health experience you think may be from the study, make sure you tell the nurses or the study investigator, [\[Dr. Doctor at \(123\) 123-4567\]](#).

(OR use the wording below for Canadian sites in this form)

By signing the consent form, you do not give up any of your legal rights and you do not release the study doctor or other participating institutions from their legal and professional duties. There will be no cost to you for the participation in this study. You will not be charged for any research procedures. If you become ill or

physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan. You will not receive any payment for participation in this study.

If you have had any injury, bad effect, or any other unusual health experience you think may be from the study, make sure you tell the nurses or the study investigator, [\[Dr. Doctor at \(123\) 123-4567\]](#).

Alternatives to Taking Part in This Study

The best known emergency care was given to you by the medics. There are no alternative treatments for your head injury except to withdraw from continued participation in the study. You can stop at any time without penalty or loss of benefits. Whether you choose to be in this study, or choose not to be in this study, will not affect your health care here at [\[insert hospital name\]](#). If you do refuse continued participation, we will not collect any more data from you. Information about your treatment that transpired up to the date and time of your treatment will still be collected.

Benefits

You may not directly benefit from this study. We cannot guarantee that there will be any benefit to you. The study may determine there is no benefit from either dose of TXA compared to salt water. It is not yet known

that TXA provides a benefit. However, you may benefit from the study if you receive TXA and it proves to be effective.

If TXA proves to be effective, the potential benefits for society are:

- Giving TXA as early as possible after head injury could help patients recover more fully after moderate to severe head injury.
- One dose of TXA 2 grams given early may help decrease bleeding in the head better than one dose of TXA 1 gram given early and followed by a second dose of TXA 1 gram given over 8 hours.

Other Information

The U.S. Department of Defense is providing grants funds for this study.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Regardless of whether or not you choose to continue in this study, you will receive the same level of care. Withdrawing from further participation in the study has no effect on how you will be treated by the doctors currently providing care.

Information available up to the point you decide not to continue participation will be retained for the study. You have the right to change your mind about participating in this study at any time. If you do change your mind, you may contact [\[name of study coordinator and phone number\]](#) or tell the doctor or nurse providing your care.

Cost, compensation, and reimbursement

There is no cost to you for participating in this study. You or your insurance will be responsible for all standard of care charges. You will not be charged for lab tests performed strictly for research purposes.

There will be no payment to you for taking part in this research study.

If you received a bill that you believe is related to your taking part in this research study, please contact [\[insert PI name\]](#) at [\[insert PI contact number\]](#) with questions.

Confidentiality

Please understand that representatives of the FDA, the [\[name of local IRB/REB\]](#), the National Institute of Health (NIH), the U.S. Army Medical Research and Materiel Command and the Resuscitation Outcomes Consortium (ROC) may review your research and/or medical records for the purposes of verifying research data, and will see personal identifiers. However, identifying information will not appear on records retained by the sponsor, with the exception of treatment and service dates. You will not be personally identified in any reports or publications that may result from this study. These records will be retained for [\[XX\]](#) years.

We do make every effort to keep the information about you. You have been assigned a code number. This code number is used on all of the data we collected. A key linking you to the code number is kept locked in a secure location and will be available only to the local site investigators. Once this study is completed, this key will be destroyed.

To help protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation for Federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your Involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Exceptions:

A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent in incidents such as child abuse, and intent to harm yourself or others.

There is a separate section in this consent form that you will be asked to sign which details the use and disclosure of your protected health information.

(OR use the wording below for sites which include the HIPAA language in this form)

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires [\[use either “your health care provider” or the actual name of the entity holding the health records\]](#) to obtain your permission for the research team to access or create protected health information about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about your relative, as described in this document, for purposes of this research study [\[if applicable, add: and for your treatment\]](#). Once [\[use either “your health care provider” or the actual name of the entity, as above\]](#) has disclosed your relative’s protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your relative’s confidentiality.

We may share your health information related to this study with other parties including U.S. and Canadian government regulatory, U.S. Army Medical Research and Materiel Command and other funding agencies, an independent research medical monitor, the [\[insert local IRB/REB\]](#), and the Resuscitation Outcomes Consortium (ROC) at the University of Washington. ROC is an emergency medicine clinical trial network which is coordinating this research.

You cannot continue to participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes [\[use “your health care provider” or the actual name of the entity, as above\]](#) to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by contacting [\[PI name\] at \[telephone number, fax number and address.\]](#) However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

The [\[insert name of the entity holding the health records\]](#) generally requires that we document in your medical record chart that you are taking part in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep the Informed Consent Document in our research files; and a copy [\[will/will not, based on local policies\]](#) be placed in your medical record chart.

To help protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation for Federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your Involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Exceptions:

A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent in incidents such as child abuse, and intent to harm yourself or others.

For additional information about this study, please visit our website at [\[local study web site link\]](#). If you have questions regarding your rights related to participation in this study, you may contact the [\[name of local IRB/REB and phone number\]](#).

Data from this study may be reported in scientific meetings, articles or other appropriate communications without your identification information.

If, during the course of the study, new information becomes available, we will provide it to you.

A copy of this consent will be placed in your medical record.

Date_____

Investigator's Name_____

Investigator's Signature_____

Subject's Statement

The study described above has been explained to me. I have had an opportunity to ask questions. If I have any other questions in the future about the research I can contact one of the Investigators listed on the first page. If I have any questions about my rights as a research subject, I can call the [\[name of local IRB/REB and phone number\]](#).

You were enrolled in a research study using an “*emergency research consent waiver*”. This process is regulated by federal and state laws. The emergency consent waiver allows researchers to screen and enroll patients with life-threatening medical conditions who cannot give informed consent and where study treatment may have to be started before informed consent from the subject or the subject's legally authorized representative can be obtained.

Study participation is voluntary. You may choose to stop being a part of this study at any time. If you choose to stop taking part in this study, no additional information will be collected. The information collected up to the time you chose to stop being in the study will remain in the research database and will be included in the data analysis. The information we collect for the study is coded to protect privacy. You will not be personally identified in any reports.

If you choose to voluntarily consent to continue in this study, please check the yes box and sign below. If you choose to withdraw from taking part in this study, please check the no box and sign below.

☐ Yes ☐ No I agree to continue to participate in this study including participating in a phone call survey 6 months after my injury to assess my recovery.

Blood will be stored for future testing related to head injury and blood clotting factors. If you choose to voluntarily consent for your blood to continue to be stored for future testing, please check the yes box and sign below. If you choose for your blood to not be stored for future testing, please check the no box and sign below.

☐ Yes ☐ No I agree to have my blood that was collected for this study stored for future testing. The specimens will be stored for future use in a de-identifiable manner such that the my identity will not be able to be known.

I have received a copy of this consent.

Date_____

Subject's Name_____

Subject's Signature_____

Parental Signature (if subject is a minor) _____

Legally Authorized Representative (LAR) Consent

Because the patient is unable to sign due to the nature of his/her illness, I am the legal guardian representing his/her wishes regarding continued participation in this study. I have had the opportunity to ask questions. If I have questions about the research, I may contact one of the Investigators listed on the first page. If I have any questions about the patient's rights as a research subject, I can call the [\[name of local IRB/REB and phone number\]](#).

The patient was enrolled in a research study using an "*emergency research consent waiver*". This process is regulated by federal and state laws. The emergency consent waiver allows researchers to screen and enroll patients with life-threatening medical conditions who cannot give informed consent and where study treatment may have to be started before informed consent from the subject or the subject's legally authorized representative can be obtained.

Study participation is voluntary. You may choose to stop the patient's being a part of this study at any time. If you choose to stop the patient's taking part in this study, no additional information will be collected. The information collected up to the time you chose to stop the patient's participation will remain in the research database and will be included in the data analysis. The information we collect for the study is coded to protect privacy. The patient will not be personally identified in any reports.

If you choose to voluntarily consent for the patient to continue in this study, please check the yes box and sign below. If you choose to withdraw the patient from taking part in this study, please check the no box and sign below.

☐ Yes ☐ No I agree for him/her to continue to participate in this study including participating in a phone call survey 6 months after his/her injury to assess my recovery.

Blood will be stored for future testing related to head injury blood clotting factors. If you choose to voluntarily consent for the patient's blood to continue to be stored for future testing, please check the yes box and sign below. If you choose for the patient's blood to not be stored for future testing, please check the no box and sign below.

☐ Yes ☐ No I agree to have his/her blood that was used for this study to be stored for future testing. The specimens will be stored for future use in a de-identifiable manner such that the patient's identity will not be able to be known.

I have received a copy of this consent.

Date_____

Legally Authorized Representative_____

Signature Legally Authorized Representative_____

For subjects and/or LAR who are unable to read and/or sign, I witness this consent.

Date_____

Witness Name_____

Witness Signature_____

Subject Consent Form if LAR or family previously consented or the subject is a minor and assent is obtained prior to hospital discharge:

You were enrolled in a research study using an “*emergency research consent waiver*”. This process is regulated by federal and state laws. The emergency consent waiver allows researchers to screen and enroll patients with life-threatening medical conditions who cannot give informed consent and where study treatment may have to be started before informed consent from the subject's legally authorized representative can be obtained.

Study participation is voluntary. You may choose to stop being a part of this study at any time. If you choose to stop taking part in this study, no additional information will be collected. The information collected up to the time you chose to stop being in the study will remain in the research database and will be included in the data analysis. The information we collect for the study is coded to protect privacy. You will not be personally identified in any reports.

This document contains the consent form signed by your legally authorized representative for your review. The consent form describes the study, (purpose, procedures, risks, benefits) in detail. Please feel free to ask any questions about this study or the consent form.

If you choose to voluntarily consent continue in this study, please check the yes box and sign below. If you choose to stop taking part in this study, please check the no box and sign below.

☐ Yes ☐ No I agree to continue to participate in this study including participating in a phone call survey 6 months after my injury to assess my recovery.

Blood will be stored for future testing related to head and blood clotting factors. If you choose to voluntarily consent for your blood to continue to be stored for future testing, please check the yes box and sign below. If you choose for your blood to not be stored for future testing, please check the no box and sign below.

☐ Yes ☐ No I agree to have my blood that was used for this study to be stored for future testing. The specimens will be stored for future use in a de-identifiable manner such that my identity will not be able to be known.

I have received a copy of the consent signed by my parent (if subject is a minor) or my Legally Authorized Representative and a copy of this Subject Consent Form.

Subject Name: _____

Subject's Signature _____ Date/Time _____

Witness Signature _____ Date/Time _____

CC: Subject's Medical Record
Subject

Sample TXA Notification of Participation letter to family of subjects who died during the study

Prehospital Tranexamic Acid Use for Traumatic Brain Injury

Month date, year

Dear [____],

We understand this letter may come at a time that is difficult for your family and we offer our condolences for your loss. We are aware a death is often an unexpected event and may have devastating personal consequences.

We want to inform you of the treatment your [son, daughter, husband, wife, (enter name)] received by [name of EMS service and hospital] from [month/date] through [month, date, year]. We want to assure you that your family member received the best medical care currently practiced for the treatment of traumatic injury. In addition to the standard treatments for trauma, your family member was entered into a research study. We are writing you now to inform you that this occurred. This was done without [his/her] prior consent because [he/she] required emergency care that could not be delayed to allow adequate consideration of informed consent.

This study was reviewed and approved by [insert name of IRB/REB]

[For those patients who died prior to having blood obtained for this research study, insert the following statement.]

No further action on your part is required.

[For those patients who had at least one blood sample obtained for this research study, insert the following statement.]

Information about the study is included with this letter entitled: Study Information Sheet – Prehospital Tranexamic Acid Use for Traumatic Brain Injury.

[Insert name of physician] is the physician responsible for the study in [Insert site/hospital name]. If you have any questions about the study, please contact us at the number provided or by contacting us at the address below:

[(xxx) yyy-yyy]
[address]

If you would like support and counseling for coping with your loss, you may call [Insert name and contact info of help line]

We apologize for this intrusion.

Respectfully,

[Name, title, address, and contact information]

Study Information Sheet Prehospital Tranexamic Acid Use for Traumatic Brain Injury

Your family member was treated for injuries including a traumatic brain injury at [name of institution]. When he/she was being treated in the accident scene and in the emergency department, he/she was unconscious

and/or unable to reliably talk with us about his/her wishes. During this time your family member was enrolled in a study called “Prehospital Tranexamic Acid Use for Traumatic Brain Injury”.

An Institutional Review Board (IRB) or Canadian Research Ethics Boards (REB) at the [name of institution] has given us permission to do this study in which subjects are enrolled without their consent. This process is called exception from informed consent for emergency research.

The purpose of this study is to determine if Tranexamic Acid (TXA) can help stop or slow the bleeding in the head after a traumatic injury compared to routine care. In this study subjects are randomly assigned (like flipping a coin) to get 1 of 2 doses of TXA or placebo, which is a salt water solution with no active medication. The dose of TXA is either an early dose of 2 grams TXA followed by placebo drip for 8 hours or split dose of 1 gram TXA followed by 1 gram TXA drip for 8 hours or placebo dose followed by placebo drip for 8 hours.

If time permitted, we may have collected and shipped blood samples to the Trauma Research Institute of Oregon, Oregon Health & Sciences University for research purposes and looked at information in their medical record; this information was recorded. The study is being done throughout the United States and Canada by an emergency medicine network called the Resuscitation Outcomes Consortium (ROC), of which Dr. [enter PI name here] is a member. This study is funded by grants received from the U.S. National Institutes of Health, US Army Medical Research and Materiel Command (USAMRMC), and other funding agencies.

Your family member’s participation in this study will help us to better understand trauma patients who experience traumatic brain injury and how we can improve the care of future trauma patients. Our study evaluates the usual care and procedures routinely performed in emergency centers throughout the United States and Canada. If you would like to know more about the study please contact [name of coordinator]

If you would like to discuss any of this further, please contact [Dr name] the doctor responsible for the study or the Research Nurse at [number here]. Also for information on a research subject’s rights and on how these studies are approved you can contact the [enter institution name here] Human subjects division at [enter contact information here].

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Consent for Blood to be Stored for Future Testing

The patient was enrolled in a research study using an “*emergency research consent waiver*”. This process is regulated by federal and state laws. The emergency consent waiver allows researchers to screen and enroll patients with life-threatening medical conditions who cannot give informed consent and where study treatment may have to be started before informed consent from the subject or the subject’s legally authorized representative can be obtained.

Study participation is voluntary. You may choose to stop the patient’s being a part of this study at any time.

The patient’s blood that was collected is being stored for future testing related to head injury and blood clotting factors. If you choose to voluntarily consent for the patient’s blood to continue to be stored for future testing,

please check the yes box and sign below. If you choose for the patient's blood to not be stored for future testing, please check the no box and sign below.

☐ Yes ☐ No I agree to have his/her blood that was used for this study to be stored for future testing. The specimens will be stored for future use in a de-identifiable manner such that his/her identity will not be able to be known.

Date_____

Legally Authorized Representative (LAR)_____

Signature Legally Authorized Representative_____

For LAR who are unable to read and/or sign, I witness this consent.

Date_____

Witness Name_____

Witness Signature_____

Appendix 3

Amendment 1: Ancillary IRB Protocol and Consent

Blood-Based Biomarkers of Injury and Outcome in the Prehospital TXA for TBI Trial

A. BACKGROUND AND SIGNIFICANCE

The public health implications of TBI cannot be overstated. At least 1.7 million people suffer TBI every year in the United States and over 50,000 people die.¹ There are currently approximately 5.3 million people living in the U.S. that require long-term or even lifelong assistance due to TBI resulting in annual direct and indirect costs of over \$76 billion.²⁻⁴ TBI also has a major impact on combat casualties and has been labeled the 'signature wound' of the Iraq and Afghanistan wars, representing an estimated 15-25% of all injuries sustained in 21st-century conflicts.⁵⁻⁷ Severe TBI is one of the leading causes of death in injured warfighters with a mortality of approximately 70%.⁸ Although our understanding of the pathophysiology of TBI has recently improved, these advances have failed to translate into a single successful clinical trial, and effective treatment of TBI remains one of the greatest unmet needs in public health.³

In addition to lack of adequate methods for identifying and quantifying brain injury, establishing a reliable prognosis early after TBI is notoriously difficult. The International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) utilized prospectively collected individual patient data from several trials in moderate or severe TBI to develop prognostic models from data available at admission.^{9,10} The strongest predictors of outcome were age, pupillary reactivity and GCS motor score (IMPACT Core Model score).¹¹ Performance of the model improved by adding both CT characteristics and secondary insults (hypotension and hypoxia) to the Core Model (IMPACT Extended Model Score).^{12,13} The IMPACT Lab Model Score further improved upon the model by adding laboratory parameters (glucose and hemoglobin).¹⁴ These prognostic models are considered to provide adequate discrimination between patients with good and poor 6-month outcomes and are currently used in clinical practice to provide prognosis prediction to families of TBI patients. In an attempt to improve the predictive power of these models, the addition of brain-specific biomarkers to the model has been examined. Using the first biomarker level obtained after TBI, addition of GFAP and SBDP145 from 45 patients with severe TBI to the Core IMPACT Model was shown to increase the predictive power for 6-month lethal outcome, increasing the R^2 from 0.214 for the Core Model alone to 0.700.¹⁵

Immediately after moderate or severe TBI, excitotoxic, ischemic, oxidative, inflammatory, and apoptotic pathways are activated, resulting in neuronal and glial cell injury and death.¹⁶ Although numerous proteins are released from the injured brain into the cerebrospinal fluid (CSF) and systemic circulation that could potentially be used as markers of cell damage after TBI, few have been characterized well enough for direct clinical use.¹⁷ Unlike other organ-based diseases such as myocardial ischemia in which rapid serum-based biomarkers are invaluable to guide diagnosis and treatment, there are currently no definitive diagnostic neurochemical markers for quantification of the degree of injury after TBI, and the paucity of well-validated biomarkers for TBI remains a major limitation to the advancement of novel treatment approaches that could improve care.

An ideal biomarker for TBI should be specific (exclusively found in the brain and accurately reflect the extent of brain injury), sensitive (highly abundant and easily detectable), and should measure therapeutic efficacy (reflect successful therapeutic intervention). There is a rapidly growing number of molecules that have been tested as potential biomarkers of TBI, however, to date no single molecule has proven sensitive and specific enough to be used clinically to predict the severity of brain injury or outcome after TBI. Of the molecules that have been tested, the best studied are neuron-specific enolase (NSE), S-100 β protein, myelin basic protein, GFAP, α -spectrin breakdown products (SBDPs), and UCH-L1.¹⁷⁻¹⁹ While NSE was originally thought to be promising as a neuronal biomarker, it was later shown to be present in red blood cells and platelets leading to confounded results in hemolyzed blood samples.²⁰ Furthermore, NSE has been shown to be elevated in trauma in the absence of TBI.²¹ S100 β is also found outside the CNS and is also influenced by extracranial injuries leading to low specificity.²² Myelin basic protein is one of the most abundant proteins in the white matter representing 30% of the protein content of myelin.²³ While it has been studied as a marker in non-

accidental pediatric trauma, there is no evidence to support its use as a diagnostic biomarker for focal and diffuse TBI. We have chosen to examine UCH-L1, GFAP and SBDP150 in this proposal based on their ability to fit the criteria for an ideal biomarker defined above as well as the strength of evidence suggesting that each biomarker reflects specific structural injury and predicts outcome, making them highly promising candidate biomarkers for TBI.

Biomarkers may provide mechanistic insight and measure treatment effect of TXA

The interventional drug being examined in the Phase II parent trial for this study is tranexamic acid (TXA). TXA is an anti-fibrinolytic medication that inhibits the conversion of plasminogen to plasmin.²⁴ There have been two randomized controlled trials examining the use of TXA in patients with moderate and severe TBI.^{25,26} Both trials utilized a different dosing regimen and both demonstrated statistical trends toward decreased progression of intracranial hemorrhage (ICH) and mortality in patients receiving TXA compared to placebo. As a result, the authors concluded that further large-scale clinical trials are needed to assess the effect of TXA on death and disability in patients with TBI. No studies to date have examined the pharmacokinetic profile of TXA use in TBI and there is currently no available method to measure therapeutic efficacy for TXA treatment in patients with TBI. Although biomarkers have not been previously measured in patients receiving TXA, the established relationship between these specific biomarkers and outcome after acute TBI suggests that they could provide a sound method to monitor response to treatment. Furthermore, based on the differential release patterns of these biomarkers and their relationship to injury pattern, relative changes in biomarker levels in response to treatment has the potential to provide insight into the mechanism of action of TXA in TBI, which is currently unknown.

While several mechanisms have been proposed to be responsible for the lower mortality and reduction in ICH growth observed in clinical trials of TXA in TBI, the mechanism involved has not been examined.²⁷ The design of the parent trial for this study will examine the effect of TXA on fibrinolytic and thrombin generation pathways to begin to understand the mechanism; however, preliminary data suggest that TXA may act by reducing the neurotoxic effects of plasmin, independent of its effect on fibrinolysis. Plasmin has been associated with potentiation of thrombin-induced neurotoxicity, degradation of the extracellular matrix, increased blood brain barrier permeability and development of cerebral edema.²⁸ Importantly, recent animal data suggest that TXA may prevent this neurotoxicity.^{29,30} While neither the parent trial nor this study will be able to thoroughly examine the mechanism of TXA in patients with TBI, identification of the relative pattern of biomarker changes in this study in response to TXA treatment could provide important insight to inform future studies that will be undertaken with the sample repository already planned in the parent trial as well as the genomic and transcriptomic repository proposed in this study.

In addition to its sensitivity and specificity, the ability of a biomarker to serve as a measure of therapeutic efficacy is an important criteria for it to be clinically useful. In order to interpret a biomarker response to treatment, an understanding of the pK profile for TXA is needed. While the pK profile for TXA following IV infusion has been described in other populations, it is unknown whether this is altered when TXA is administered via bolus or continuous infusion in patients with TBI.³¹⁻³³ Additionally, the optimal TXA dosing regimen for patients with TBI is not known and no consensus exists about the ideal targeted plasma concentrations needed to inhibit fibrinolysis. As a result, the parent clinical trial for this study was designed to include 2 different dosing arms of TXA compared to placebo (arm one: 1-gram bolus followed by 1-gram infusion; arm two: 2-gram bolus followed by placebo infusion, arm three: placebo bolus and placebo infusion). It is important to note that the analysis for the primary endpoint (GOS-E at 6 months) of the parent trial will be a comparison of both treatment arms combined compared to placebo. For these reasons, the association between the pK profiles, biomarker levels and clinical outcome are needed to interpret the biomarker response to treatment as well as to inform the results of the parent trial. As an example, if a longer half-life is shown to be associated with a favorable biomarker profile, this would potentially suggest a benefit for redosing or extending the TXA infusion period. Alternatively, if the higher maximum concentration achieved in the 2-gram bolus arm is associated with a favorable biomarker profile, this would help inform the most efficacious dosing

regimen in the future. The opportunity to examine the biomarker response in the two different dosing arms of this trial with the associated pK profile will enable us to

determine if these candidate biomarkers can be used as a measure of treatment effect for TXA in patients with TBI and potentially incorporate them in a follow-up phase III trial for this purpose.

Creation of a genomic and transcriptomic repository for future biomarker development

While the biomarkers of structural brain injury proposed in this study are the most promising markers of TBI currently available, there remains an incomplete understanding of post-injury cellular and molecular changes after TBI.³⁴ Examination of RNA and DNA expression is rapidly increasing the ability to examine molecular changes after TBI. As an example, MicroRNAs (miRNAs) are short noncoding RNAs that modulate protein expression by antagonizing mRNA translation that have a powerful role in the regulation of gene expression and cellular function.³⁵ Because a single miRNA can block translation of many mRNAs, they are very potent regulators at the network level. Thus, global patterns of change in both the injured tissue as well as the circulation can be determined. Recent miRNA microarray studies indicate that pathways such as apoptosis, inflammation and cell proliferation are among the most commonly affected in CNS injuries, and that changes in these pathways are conserved across CNS injuries to stroke.³⁶ This type of information is crucial to providing insight into therapeutic targets for future TBI trials. Because miRNA levels are altered after TBI and these changes have a profound effect on downstream targets, restoration and inhibition of miRNA activity presents the opportunity to modulate these cellular processes. In order to realize the potential for miRNA, validation of findings from animal models will need to be performed in large human samples. By creating a repository of miRNA, mRNA and DNA from patients with TBI very early after injury, future investigators will have the opportunity to further explore both miRNA-based and genome-based therapies and potentially improve outcome after TBI. It is important that we leverage the significant resources already committed for this large clinical trial now, in order to support a broad-range of studies in the future that could lead to potentially lead to new biomarkers and new treatment targets for TBI.

B. SPECIFIC AIMS

Specific Aim 1: To determine if initial values, or trends in serially measured circulating brain-specific biomarkers (GFAP, UCH-L1, SBDP150) are associated with the presence of intracranial hemorrhage (ICH), TBI pattern and severity, and long-term outcome after moderate or severe acute TBI.

Hypothesis 1.1: Elevated biomarker levels measured within 2 hours of TBI are associated with ICH on initial computed tomography (CT) scan and less favorable Rotterdam and Marshall CT classification scores.

Hypothesis 1.2: Biomarkers that remain elevated or subsequently increase during the first 48 hours after injury are associated with ICH progression and a less favorable outcome as measured by the GOS-E at 6 months.

The primary aim examines whether elevated biomarker levels accurately identify the presence of ICH, as well as the specific pattern (focal versus diffuse) and severity of TBI. It will also determine if sustained biomarker levels or an increasing trajectory of early biomarker levels reflect worsening ICH and unfavorable outcome. These data would be extremely valuable to determine clinically relevant endpoints including identification of appropriate patients for inclusion into clinical TBI trials and targeting patients for more intensive intervention.

Specific Aim 2: To determine if circulating brain-specific biomarkers (GFAP, UCH-L1, SBDP150) are associated with treatment arm allocation, serum TXA level, and long-term outcome as measured by the GOS-E 6 months after injury in moderate or severe acute TBI.

Hypothesis 2.1: In TXA treated patients compared to placebo, decreased circulating biomarkers measured serially during the first 48 hours after TBI are associated with a favorable long-term outcome.

Hypothesis 2.2: In TXA treated patients, serum TXA levels are inversely associated with circulating biomarkers and directly associated with long-term outcome.

The secondary aim examines whether serum TXA levels are associated with circulating biomarkers. If early biomarker levels are shown to be a measure of treatment response, this would inform future treatment paradigms for the use of TXA in TBI. By identifying patients who benefit most from TXA treatment and quantifying the treatment response, these biomarkers could impact treatment decisions. Knowledge of the pharmacokinetic and biomarker profiles associated with a favorable outcome would help establish the optimal dosing regimen for future clinical trials, including a follow-up phase III trial to the Prehospital Tranexamic Acid Use for Traumatic Brain Injury (Prehospital TXA for TBI) Trial.

Specific Aim 3: To determine if circulating brain-specific biomarkers (GFAP, UCH-L1, SBDP150) improve long-term outcome prediction after moderate or severe acute TBI.

Hypothesis 3: Elevated circulating biomarkers measured within 2 hours of TBI improve outcome prediction as measured by the Disability Rating Scale (DRS) and Glasgow Outcome Scale-Extended (GOS-E) at 6 months.

The tertiary aim incorporates biomarker and clinical data obtained early after injury in patients enrolled in the control arm of a large prehospital clinical trial to determine if adding biomarkers to the well-validated IMPACT core model (including age, GCS motor score, pupillary reactivity) improves 6-month outcome prediction. This would provide a basis to inform treatment decisions and inclusion criteria for enrollment in future clinical trials.

In addition to the aims above, we propose to leverage the resources of this large clinical trial to create a genomic and transcriptomic specimen repository from sequential time points very early after injury in patients enrolled in the Prehospital TXA for TBI Trial. This unique repository from patients with moderate or severe TBI will allow future examination of systemic genomic and transcriptomic changes that occur after TBI. Future studies resulting from this repository have the potential to provide diagnostic, prognostic and therapeutic insight that would significantly advance the understanding of the pathophysiology of TBI.

C. INNOVATION

The Prehospital TXA for TBI Trial is the first large clinical trial to randomize patients to receive a potential therapeutic drug for moderate or severe TBI in the prehospital setting within 2 hours of injury. Approximately 1000 patients will be enrolled at 10 centers across the US and Canada under an FDA Exception from Informed Consent to determine if early administration of TXA is effective for improving outcome measured 6 months after injury. Because patients will be randomized by first-responders at the injury scene and followed for 6 months, this provides a unique opportunity to validate the most promising brain-specific serum biomarkers.

This will be the first study to prospectively examine the diagnostic and prognostic value of circulating brain-specific biomarkers measured very early after injury in patients enrolled in the prehospital setting of a large randomized controlled trial of moderate and severe TBI. While studies have shown that biomarkers of structural brain injury measured in serum are associated with outcome after TBI, they are not yet established for clinical use to reliably detect and assess the degree of brain injury or predict outcome. **With this study we will be able to refine the diagnosis of TBI to enable early identification of specific patterns of brain injury that can be linked to appropriate therapeutic interventions for targeted inclusion into clinical trials. Furthermore, we may expand upon existing prediction models to support both clinical practice and TBI research, including the design and analysis of randomized trials. In addition, we may also for the first time establish brain-specific biomarkers as an effective method of monitoring response to**

treatment in TBI that could have widespread use both clinically and in interventional TBI trials. Each of these aims will contribute to the success of future clinical trials in TBI including the follow-up phase III trial of the Prehospital TXA for TBI Trial. Finally, by leveraging the resources of this large clinical trial to obtain specimens very early after injury, we will create the first large repository integrating genomic and transcriptomic information with comprehensive clinical, laboratory and imaging data from patients with moderate and severe TBI. This repository will serve to expand TBI related research to support new biomarker development as well as a broad range of studies that will significantly advance our understanding of the pathophysiology of TBI.

D. STUDY DESIGN

The proposed study to examine the relationship between serum levels of biomarkers of structural brain injury and clinical outcome will be carried out in the cohort of approximately 1000 patients with moderate and severe TBI enrolled in the Prehospital TXA for TBI clinical trial (ClinicalTrials.gov ID: NCT01990768). This clinical trial will be conducted using the infrastructure of the Resuscitation Outcomes Consortium (ROC). ROC is a multicenter network funded by federal organizations in the United States and Canada (including the DoD and NHLBI) to conduct clinical trials targeting cardiac arrest and life-threatening trauma.³⁷ The Prehospital Tranexamic Acid for Traumatic Brain Injury Trial will be the 11th prehospital randomized trial conducted by ROC and the third trial in patients with TBI. The following is a brief overview of the trial.

The Prehospital TXA for TBI Trial is a randomized, double-blind, placebo-controlled phase II multicenter trial in which approximately 1000 patients with moderate or severe TBI will be randomized (1:1:1) to one of three arms:

- 1-gram TXA prehospital bolus followed by an in-hospital 1-gram 8 hour infusion
- 2-gram TXA prehospital bolus followed by an in-hospital placebo infusion
- Placebo prehospital bolus followed by an in-hospital placebo infusion

The following are the primary inclusion criteria and outcome measures for the parent trial:

Inclusion criteria:

- Blunt and penetrating traumatic mechanism of injury consistent with TBI
- Prehospital GCS ≤ 12 prior to administration of sedative and/or paralytic agents with at least one reactive pupil
- Pre-hospital systolic blood pressure ≥ 90 mmHg
- Estimated time from injury to hospital arrival of < 2 hours

Primary outcome:

- Disability at 6 months based on the GOS-E

Secondary outcomes:

- Clinical outcomes: neurologic outcome at discharge, 28-day survival, frequency of neurosurgical interventions, ventilator-free, ICU-free, and hospital-free days
- Radiographic outcomes: intracranial hemorrhage progression, Marshall CT and Rotterdam CT classification scores
- Safety outcomes (seizures, cerebral ischemic events, myocardial infarction, deep venous thrombosis, pulmonary embolism)
- Mechanistic outcomes (coagulation pathway mediator analysis and viscoelastic testing using thromboelastography [TEG])

Integration of this biomarker study with the Prehospital TXA for TBI Trial

The inclusion criteria for this study will be the same as the inclusion criteria for the Prehospital TXA for TBI clinical trial. Eligible patients must be at least 15 years old and have a GCS of 12 or less with at least one reactive pupil. Patients with hypotension, cardiopulmonary arrest or seizures prior to randomization will be excluded. The Prehospital TXA for TBI Trial will enroll patients in the prehospital setting and precludes the

ability to obtain informed consent at the time of enrollment. The trial qualifies for the “Exception From Informed Consent Required for Emergency Research” outlined in FDA regulation 21CFR50.24. The Institutional Review Board (IRB) for the ROC Clinical Trials Center at the University Of Washington has reviewed and approved the informed consent procedures for the parent trial. Additional sites (including the OHSU Clinical Site and Clinical Coordinating Center) have contingent IRB approval and are ready to begin community consultation. The remaining clinical sites are in the process of obtaining IRB approval. In order to seamlessly integrate the biomarker component of the protocol into the parent study, it has been incorporated into the required community consultation presentations. Consent for this ancillary study will be incorporated as follows:

Consent for non-genetic biomarker tests

The parent TXA Study consent includes language that allows for future use of blood to be collected (non-genetic). No additional specimen collection or consent is needed for the brain-specific biomarkers and the pK studies as outlined in the specific aims.

Consent for the genomic and transcriptomic repository

A separate consent and additional blood collection is required for creation of the genomic and transcriptomic specimen repository. A consent form has been created that specifically relates to this repository and is separate from the overall TXA study consent. Participation in both studies will have two consent forms.

Recruitment timeline for the Prehospital TXA for TBI Trial

Recruitment in the Prehospital TXA for TBI Trial is anticipated to begin in October 2014 based on completion of Community Consultation activities at each site. The trial is expected to enroll 1002 patients at 10 clinical sites over a one-year period. Since all required regulatory and community consultation and notification for this ancillary study will be in place prior to funding, if funded during the current NIH cycle with this expedited funding timeline beginning December 1st 2014, enrollment for this study will approximately coincide with the beginning of enrollment for the parent trial. This will allow full biomarker and pK analyses as these samples will be collected as part of the parent trial. Depending on the start of the trial, the maximum number of patients eligible for the genomic and transcriptomic samples will range between 730 (based on an October 1st trial start date) and 886 (based on a November 1st start date). This will ensure a robust sample size for establishing the repository.

Time points for sample collection

We will use the biomarker levels obtained from the earliest time point (arrival to the ED) based on our preliminary data that showed a strong correlation between early biomarker measurements and outcome. Based on data from the ROC Hypertonic Saline Study, we anticipate that most of the initial blood samples will be obtained approximately 90 minutes after TBI.³⁸ We will also measure biomarker levels at 6, 12, 24, and 48 hours to examine the evolution of biomarker release in relation to outcome. We will measure the TXA pK profile at these same time points as the biomarker profile will be important in determining the response to TXA treatment. This will also help determine whether the effect of TXA treatment can be monitored by measuring biomarker levels during the first 48 hours after TBI, potentially establishing biomarkers as a routine method of determining effective treatment and guiding decisions related to additional interventions.

Sample collection

Biomarker and pK sample analysis will be done on blood already being collected as part of the main protocol. As a requirement for participation in the Prehospital TXA for TBI Trial, all sites will have research coordinators on-site 24 hours per day to ensure the initial blood sample is obtained as soon as possible after ED arrival, and to ensure the in-hospital TXA dose is administered in a timely fashion. All attempts will be made to obtain study samples at the pre-specified time intervals. Samples at times 0, 6, and 12 hours must be collected within +/- 30 minutes. Sampling at 24 and 48 hours will be collected within +/- 2 hours. In the event that samples cannot be collected in this time frame, documentation regarding the reason will be noted on the data collection forms. In addition to samples collected as part of the parent study, each subject will provide one blood sample collected in a PAXgene tube (2.5 mL) for RNA stabilization on arrival to the Emergency Department (time 0) and 6, 12, 24, and 48 hours after study randomization. Another sample (3.0 mL) will be

collected in an Acid Citrate Dextrose (ACD) tube for preservation of genetic material at admission. All samples drawn for research purposes will be identified by the study number, the site identification number and date/time of collection. No personal identifying information will be included on the samples processed for research purposes. Samples from participating sites will be frozen, batched, and shipped to the OHSU Clinical Coordinating Center. OHSU will be the repository guardian for the samples and results. The procedures for collection for all samples including DNA and RNA preservation are currently being incorporated into the Prehospital TXA for TBI Trial Manual of Operations. Procedures for DNA and RNA specimen collection and processing will follow the "NINDS Repository Biomarkers Discovery Samples Resource Laboratory Manual Guidelines."³⁹ The OHSU Clinical Coordinating Center will manage initial sample storage and tracking. Samples for biomarker analysis will be shipped in batch to Dr. Papa's laboratory at Orlando Regional Medical Center. Specimens will be transported to the OHSU Bioanalytical Shared Resource/Pharmacokinetics Core for TXA pK analysis using liquid chromatography tandem mass spectrometry. PAXgene (mRNA and miRNA) and ACD (DNA) collection vials will be transported to the Integrated Genomics Laboratory at OHSU for creation of the repository.

Biomarker assays

Banyan has extensive experience in assay development and validation including expertise in developing high-affinity antibodies to proteins. For the UCH-L1 assay, a mouse monoclonal antibody (as capture antibody) and a rabbit polyclonal antibody (as detection antibody) are used in combination with a commercially available anti-rabbit IgG-HRP (Amersham) as labeling antibody. The capture and detection antibody have been developed to full-length recombinant human UCH-L1 protein. A detailed description of the assay methods has been published by Dr. Papa.⁴⁰ The GFAP and SBDP150 assays follow an identical outline, but employ different biomarker-specific capture and detection antibodies. For the GFAP assay, a mouse monoclonal antibody (as capture antibody) and rabbit polyclonal antibody (as detection antibody) are used. Capture and detection antibodies were generated to full-length human recombinant GFAP. The SBDP150 assay uses a goat polyclonal antibody as capture antibody and a mouse monoclonal horseradish peroxidase conjugated antibody as detection antibody.

TXA pK profile analysis

Two separate cohorts for the pK analysis will be established as described below:

Extensive sampling cohort

The first 100 patients enrolled at the OHSU clinical site will have blood drawn at the following time points based on the prehospital bolus TXA dose: 2, 3, 4, 6, 8, 9, 10, 12, 24, and 48hrs. This will enable a robust pK profile to be established with greater confidence in estimated pK parameters. Serum will be isolated within 1 hour of blood collection, frozen, and shipped to the OHSU shared Bioanalytical Core Laboratory for quantifying serum TXA levels using a highly sensitive and specific liquid chromatography-mass spectrometry assay. Serum levels will be fitted against time to construct pK profiles and estimate PK parameters. The following PK parameters will be generated: area under the curve from time 0 to 48 hour (AUC_{0-48}), AUC from 0 to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$), clearance (CL/F), volume of distribution (V_d/F).

Limited sampling cohort

Samples will be obtained from 5 time points for all patients (arrival to ED, 6, 12, 24, and 48 hours after study randomization). This limited sampling scheme will enable an estimate of PK parameters (with less confidence than in the extensive sampling group), with the exception of $t_{1/2}$ which will remain robust. Analyses will focus on the extensive sampling cohort with the exception of $t_{1/2}$ which will be extended to all subjects.

E. ANALYSIS PLAN

Analysis plan for the aims of this study:

Hypothesis 1.1: Elevated biomarkers measured within 2 hours of TBI more accurately predict ICH and brain injury pattern and severity on initial computed tomography (CT) scan than GCS.

As preliminary analyses, we will use logistic regression to examine whether initial levels of brain-specific biomarkers (GFAP, UCH-L1, SBDP150) are associated with the presence of ICH on initial CT scan in subjects in the placebo arm. In patients with evidence of brain injury (Marshall score >1), we will also examine the association with mass lesions vs diffuse injury.

To examine whether initial brain-specific biomarker levels (GFAP, UCH-L1, SBDP150) improve upon GCS in predicting presence of injury, we will create Receiver Operating Characteristic (ROC) curves that describe the sensitivity and specificity profiles of each individual biomarkers for predicting the presence of ICH on initial CT scan. We will compute the area under the ROC curve (AUC) as a summary measure of the predictive ability of each biomarker and compare it to the AUC based on the GCS alone. A confidence interval for the difference in AUCs will be computed using Delong's method.⁴¹

To examine whether combinations of the initial brain-specific biomarker levels (GFAP, UCH-L1, SBDP150) improves upon GCS or whether one or more of these biomarkers together with GCS improves upon the GCS alone in predicting presence of injury or injury pattern, we will adopt a 10-fold cross-validation approach⁴² to develop multivariable predictive models based on combinations of biomarkers and combinations of biomarkers and GCS. Levels of the three biomarkers and the GCS will be candidate variables in these models, which will relate the probability of ICH outcome, p , to biomarkers and GCS and possibly their interactions $x_1, \dots, x_n$, as follows: $\log(p/(1-p)) = b_0 + b_1x_1 + \dots + b_nx_n$.

Without the need to reserve a separate validation data set, ten-fold cross-validation reduces the optimistic bias inherent in evaluating the AUC based on the same data used to fit the model since the evaluations depend on the tent of the data not used to fit the model. We will pick the best predictive model size based on the maximal cross-validated AUC estimate, and our final predictive model will be based on the model of this size that maximizes the likelihood for the full sample. Secondary analyses to obtain models with high clinical utility will use this same cross-validation approach to identify and evaluate good tree-based models using classification and regression tree (CART) methodology.⁴³ We will also fit the predictive model to all subjects in the three treatment arms, and examine interaction terms that allow for different associations in the different arms. If no significant interactions are detected, we will develop a single predictive model using data from subjects in all treatment arms combined.

Hypothesis 1.2: Biomarkers that remain elevated or subsequently increase during the first 48 hours after injury are associated with ICH progression and an increased 28-day mortality.

Additional goals under Specific Aim 1 are to examine whether there are associations between trends in serial biomarker levels during the first 48 hours after injury and two outcomes: ICH progression and 28-day mortality. To examine these relationships we will treat the biomarker level as the outcome and use linear mixed models to account for the correlation of the multiple biomarker measurements within subjects. The mixed models will allow us to test whether both types of clinical measures are associated within-subject biomarker mean levels and slopes over time.

Hypothesis 2.1: In TXA treated patients compared to placebo, decreased biomarkers measured serially during the first 48 hours after TBI are associated with a favorable long-term outcome.

Preliminary analyses will use linear mixed models, as above, to examine whether treatment group is

related to mean levels and subject-specific slopes in serial measurements of brain-specific biomarkers (GFAP, UCH-L1, SBDP150) over the first 48 hours after injury. We will also examine whether favorable outcome of GOS-E at six months is related to mean levels and slopes in biomarkers within 48 hours of injury.

Hypothesis 2.2: In TXA treated patients, serum TXA levels are inversely associated with circulating biomarker levels and directly associated with long-term outcome.

In TXA-treated patients, we will use linear mixed models to examine whether pharmacokinetic (pK) parameters (AUC, Cmax, Tmax, T_{1/2}, clearance, and Vd) are associated with mean levels and slopes of serial levels of brain-specific biomarkers (GFAP, UCH-L1, SBDP150) during the first 48 hours after injury. Interaction terms with treatment group will allow us to test whether these associations differ by dosing regimen. We will also use logistic regression to examine whether pK parameters (AUC, Cmax, Tmax, t_{1/2}, clearance, and Vd) in the two dose groups are associated with favorable clinical outcome at six months based on the GOS-E. We will then (with interaction terms) examine whether these associations differ by dosing regimen.

Subsequent analyses will examine the extent to which serial biomarker levels during the first 48 hours after injury explain the association between PK parameters (AUC, Cmax, Tmax, t_{1/2}, clearance, and Vd) and 6-month GOS-E among those treated with TXA, and to what extent they explain the association between treatment group (placebo, bolus-only, and bolus plus infusion) and 6-month GOS-E. Taking the treatment group comparison as the example, we will fit logistic regression models relating dummy variables for the two treatment groups to the outcome of 6-month GOS-E < 5 both with and without adjustment for serial biomarker levels. We will then compare adjusted and unadjusted results from these models to estimate whether an important proportion of the treatment differences are explained by the biomarker levels. One minus the ratios of these two coefficients will

be used to estimate the proportion of the estimated association that is explained by the biomarkers. Confidence intervals for these explained proportions will be obtained using the bootstrap.⁴⁴ Similar analyses will examine to what extent the biomarkers explain the pK parameter- 6-month GOSE associations, after adjustment for and possible interaction with dosing regimen.

Hypothesis 3: Elevated circulating biomarkers measured within 2 hours of TBI improve outcome prediction as measured by the DRS and GOS-E at 6 months.

Among controls, we will relate initial brain-specific biomarker levels (GFAP, UCH-L1, SBDP150) to poor clinical outcome (GOS-E < 5) at six months by fitting logistic regression models. Using single-variable linear logistic models, preliminary descriptive analyses will compute the crude OR for poor outcome associated with a one standard deviation difference in the biomarker and a 95% confidence interval.

To develop a multivariable predictive logistic model including brain-specific biomarkers that might improve upon the IMPACT Core Model,^{9,10} we will adopt a 10-fold cross-validation approach like the one to be used under the analysis for Specific Aim 1. All variables in the IMPACT Core model together with initial values of GFAP, UCH-L1, and SBDP150 and all squares of continuous variables two-way interactions between variables will be candidate variables for this model. As for analyses under Specific Aim 1, model size will be chosen by cross-validation, and the best final predictive model of that size will be identified from all the control-group subjects. Secondary analyses to obtain models with high clinical utility will also use this cross-validation approach to identify and evaluate good tree-based models using CART methodology.

As an exploratory analysis, we will also fit our predictive model to the combined data including control-arm and treatment-arm subjects, and allow interactions between TXA treatment (placebo, bolus-only, and bolus plus infusion) and all variables in the predictive model from controls. Significant interaction terms in these models could be used to generate hypotheses about the types of patients who benefit most from treatment for examination in future trials. If no significant interactions are detected, we will develop a single predictive model to data from subjects in all treatment arms combined.

Sample size justification

The sample size for primary analyses for the TXA clinical trial is 963 eligible patients (321 per group) assuming (based on the ROC Hypertonic Saline (HS) Trial)³⁸ 4% of the 1002 target enrollment will have the treatment kit opened and not given. Based on prior experience in subjects with severe TBI (GCS $\leq$ 8) from the same clinical sites and hospitals for the TXA trial (that participated in the HS trial), head CT scans were obtained for more than 95% of subjects. In this cohort between 59% and 88% of subjects had a Marshall score > 1 (depending on site). We anticipate slightly lower rates in the TXA trial based on the eligibility criteria including both moderate and severe TBI (GCS $\leq$ 12). To calculate the power we will have to determine if a biomarker combined with GCS improves upon GCS alone as a predictor of ICH, we simulated the power to detect odds ratios for the association of a one standard deviation higher biomarker value in a logistic model that also includes GCS based on a control-group sample size of $.90 \times 321 = 289$. Under a variety of correlations between GCS and biomarker ranging from $\pm .1$ to $\pm .5$, ORs for the association of a 1 SD lower GCS ranging from 1.2 to 2.0, and average probabilities of ICH ranging from .6 to .8, we consistently had 80% power or more to detect an OR of 1.5 associated with a one SD higher biomarker value (in some settings we had more than 80% power to detect an odds ratio of 1.4). These are consistent with ORs associated with these biomarkers that have been found in a number of smaller studies.⁴⁵⁻⁴⁸

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Sample – Genetics Consent/Notification

[\[Insert name of institution\]](#)

Continued Participation Consent/Notification Form

Blood-based Biomarkers of Brain Injury and Clinical Outcome in the Prehospital TXA for TBI Trial

Investigators

[\[List name, title and phone numbers\]](#)

Sample – Genetic Clinical Research Consent and Authorization Form

PURPOSE:

“You” throughout this document refers either to yourself, as the patient, or the person for whom you are the legally authorized representative (LAR). You have been invited to be in this research study because you have a traumatic brain injury and were enrolled in the Prehospital Tranexamic Acid Use for Traumatic Brain Injury study. The purpose of this study is to better understand if changes in brain chemicals in those with traumatic brain injury are associated with certain genes. We will investigate genetic factors that may affect how the brain reacts to traumatic injury. We hope that this information will allow us to better understand how genes affect a person’s response to traumatic brain injury.

If a gene or genes can be found, treatment of traumatic brain injury may be improved.

Genes are the units of DNA--the chemical structure carrying your genetic information--that determine many human characteristics such as the color of your eyes, your height, and whether you are male or female.

Genetic markers used to identify individual’s response to brain injury have not been identified. Improved identification could save millions of dollars in healthcare costs and save thousands of lives. This study is important to design future care of those suffering from traumatic brain injury.

The blood samples provided by you will be analyzed in the laboratory to determine whether there are differences in the genes of people who have a traumatic brain injury.

This study will enroll approximately 1000 subjects across the United States and Canada. The study will enroll approximately 100 subjects here at [institution name].

PROCEDURES:

You have been enrolled in this research study because you have had a traumatic brain injury and were enrolled in the Prehospital Tranexamic Acid Use for Traumatic Brain Injury study. Blood is drawn for genetic testing when you arrive at the hospital and at 6, 12, 24, and 48 hours if you are still in the hospital. At each time point, about 1 teaspoon (5.5 mL) of blood is drawn. These samples will be used to look for changes to genes that happen after traumatic brain injury. Your permission is needed to keep any samples collected, and to draw any samples not already collected.

If you have any questions regarding this study now or in the future, contact [site investigator (XXX) XXX-XXXX] or other members of the study team at (XXX) XXX-XXXX.

SUBJECT ACCESS TO GENETIC INFORMATION:

The results of these studies will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

If we discover new information that is important for your health care, either in this study or the future, you will be asked whether you wish to receive the results. You may be required to have the test repeated in a clinical laboratory. Because genetic information is complex and sensitive, the results should be discussed with a genetic counselor or your primary care giver who can answer your questions or discuss your concerns. You would be responsible for all costs associated with having the test repeated and visiting a doctor or genetic counselor to discuss the results.

RISKS AND DISCOMFORTS:

If we are unable to collect a blood sample from an existing IV line, we will need to draw blood from a vein in your arm or hand. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, an infection, or fainting.

Efforts will be made to keep your personal information as described in the CONFIDENTIALITY section, but we cannot guarantee total privacy.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

Although we have made efforts to protect your identity, there is a small risk of loss of confidentiality. If the results of these studies of your genetic makeup were to be accidentally released, it might be possible that the information we will gather about you as part of this study could become available to an insurer or an employer, or a relative, or someone else outside the study. Even though there are certain genetic discrimination protections in both Oregon law and federal law, there is still a small chance that you could be harmed if a release occurred.

BENEFITS:

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

ALTERNATIVES:

You may choose not to be in this study.

CONFIDENTIALITY:

We will take steps to keep your personal information, but we cannot guarantee total privacy.

We will create and collect health information about you as described in the Purpose and Procedures sections of this form. Health information is private and is protected under federal law and [state] law. By agreeing to be in this study, you are giving permission (also called authorization) for us to use and disclose your health information as described in this form.

The investigators, study staff, and others at [site institution] may use the information we collect and create about you in order to conduct and oversee this research study. We may release this information to others outside of [site institution] who are involved in conducting or overseeing research, including:

- The National Institute of Health (NIH)
- The U.S. Army Medical Research and Materiel Command (USAMRMC)
- The Food and Drug Administration (FDA)
- Resuscitation Outcomes Consortium (ROC) at the University of Washington
- Canadian Regulatory Agencies
- An Independent Research Medical Monitor

We will not release information about you to others not listed above, unless required or permitted by law. We will not use your name or your identity for publication or publicity purposes, unless we have your special permission.

To help protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation for Federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your Involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Exceptions:

A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent in incidents such as child abuse, and intent to harm yourself or others.

Under state Law, suspected child or elder abuse must be reported to appropriate authorities.

[Site institution] complies with state requirements for reporting certain diseases and conditions to local health departments.

When we send specimens or information outside of [site institution], they may no longer be protected under federal or state law. In this case, your specimens or information could be used and re-released without your permission.

Study ID numbers will be assigned to each participant. Only study IDs will be used on study related materials, including data and biological samples. Only the investigators and people involved in the conduct of the study will be authorized to link the code number to you. All study and research files will be maintained in locked files and destroyed at the completion of the study. Publications and presentations resulting from this study will be

reported as aggregate data with no personal identifiers. No names of participants will be released unless written permission has been received from the study participant.

COMMERCIAL DEVELOPMENT:

Samples and information about you or obtained from you in this research may be used for commercial purposes, such as making a discovery that could be patented or licensed to a company. There are no plans to pay you if this happens. You will not have any property rights or ownership or financial interest in or arising from products or data that may result from your participation in this study. Further, you will have no responsibility or liability for any use that may be made of your samples or information.

COSTS:

There will be no cost to you or your insurance company to participate in this study.

LIABILITY:

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact [site investigator at (XXX) XXX-XXXX] or [site coordinator at (XXX) XXX-XXXX].

This federally funded study does not have the ability to provide compensation for research-related injury. If you are injured or become ill from taking part in this study, it is important to tell your study doctor. Emergency treatment may be available but you or your insurance company will be charged for this treatment.

PARTICIPATION:

If you have any questions regarding your rights as a research subject, you may contact the [site institution] Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. You do not have to allow the use and disclosure of your health information in the study, but if you do not, you cannot be in the study.

If you do join the study and later change your mind, you have the right to quit at any time. This includes the right to withdraw your authorization to use and disclose your health information. If you choose not to join any or all parts of this study, or if you withdraw early from any or all parts of the study, there will be no penalty or loss of benefits to which you are otherwise entitled, including being able to receive health care services or insurance coverage for services. Talk to the investigator if you want to withdraw from the study.

If you no longer want your health information to be used and disclosed as described in this form, you must send a written request or email stating that you are revoking your authorization to:

Site Investigator, MD

Site Institution

Site Address

Site Email

Your request will be effective as of the date we receive it. However, health information collected before your request is received may continue to be used and disclosed to the extent that we have already acted based on your authorization.

If in the future you decide you no longer want to participate in this research, we will ask for your permission to use the information we have collected. If you do not give permission, we will destroy the information.

The samples and information we will collect from you will be stored at [site institution]. They will be stored with a coded identifier to protect your privacy.

We will give you any new information during the course of this research study that might change the way you feel about being in the study.

Your health care provider may be one of the investigators of this research study and, as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

We will give you a copy of this signed form.

Printed Name of Subject (If 18 or older)	Signature of Subject (If 18 or older)	Date
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Printed Name of Subject (If 15 to 17 years old)	Signature of Subject (If 15 to 17 years old)	Date
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Printed Name of Parent, Guardian, or Legally Authorized Representative (if subject unable to provide consent or under 18 years old)	Signature of Parent, Guardian, or Legally Authorized Representative (if subject unable to provide consent)	Date
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Relationship to subject

Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date
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