(TXA-Dosing)

Tranexamic Acid Dosing for Major Joint Replacement Surgery
Prospective cohort study at Sunnybrook Health Sciences Center (SHSC)

Protocol Number: *1567*

Principal Investigator: *Dr. Angela Jerath*

Regulatory Sponsor: Sunnybrook Research Institute
Funding Agency: Sunnybrook AFP Association through the Innovation Fund of the Alternative Funding Plan from the Academic Health Sciences Centre of Ontario
Investigational Product: *Tranexamic acid*

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SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the sponsor:

Name: *(Print)*	Dr. Angela Jerath
Title: *(Print)*	Principal Investigator
Signature:	
Date of Approval: *(yyyy-mmm-dd)*	

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Principal Investigator:

Name: *(Print)*	Dr. Angela Jerath
Title & Institution: *(Print)*	Staff Anesthesiologist, SHSC
Signature:	
Date of signature: *(yyyy-mmm-dd)*	

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Event/Adverse Experience
CC	Coordinating Centre
CIOMS	Council for international Organizations of Medical Sciences
CKD	Chronic Kidney Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CCTS	Centre for Clinical Trial Support
EC	Ethics Committee
EDC	Electronic Data Capture
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Authorities
pCRF	Paper Case Report Form
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetic
PM	Product Monograph
QI	Qualified Investigator
REB	Research Ethics Board
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event/Serious Adverse Experience
SHSC	Sunnybrook Health Sciences Centre
SOP	Standard Operating Procedure
SRI	Sunnybrook Research Institute

SUADR	Serious and Unexpected Adverse Drug Reaction
TMF	Trial Master File
TXA	Tranexamic Acid

PROTOCOL SUMMARY

Protocol Title (Short Title)	Tranexamic acid dosing for major joint replacement surgery *(TXA-Dosing)*
Protocol Number	*1567*
Phase	II
Study Design	Prospective cohort study conducted at Sunnybrook Health Sciences Centre (SHSC). This study will investigate the optimal TXA dose for hip and knee joint replacement surgery. 20 participants (10 in each group) will be included and stratified into two groups: • Group I: participants with glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 (and dialysis) • Group II: participants with GFR ≥ 60 mL/min/1.73m^2 Participants will be given single intravenous bolus of TXA 20 mg/kg over 15 min after induction of spinal (or other regional technique) or general anesthesia as per standard of care. Blood samples will be drawn from an arterial or venous catheter line at following time points after induction of anesthesia: baseline/pre-TXA administration, 5 min, 15 min, 30 min, 1h, 1.5h, 3h, 6h+/-2 and 12h+/-4 post-bolus.
Study Duration	2 years
Setting	Single-centre
Sample Size	20
Main Inclusion Criteria	(1) Adults > 18 years old (2) Elective unilateral hip or knee joint replacement.
Primary Outcome(s):	Measurement of serial blood plasma TXA concentration to build a Pharmacokinetic (PK) model and dosing regimens for patients within both groups
Secondary Outcome(s):	(1) Intraoperative blood loss and transfusion (2) % reduction in pre- and postoperative hemoglobin

	(3) Postoperative creatinine, GFR and other plasma renal biomarkers (for e.g., NGAL, SUPAR, cystatin) (4) In-hospital mortality (5) Hospital length of stay
Investigational Product and Planned Use	After spinal (or other regional technique) or general anesthesia, a single intravenous bolus of TXA 20 mg/kg will be given (as per our standard of care) over 15 minutes.
Statistical Analysis:	Continuous variables will be summarized using median (interquartile range) and studied using a Mann Whitney U test. Categorical variables will be summarized using frequency (%) and studied using a Chi-square. These analyses will be performed using SAS v9.6 (US).

1 KEY ROLES AND CONTACT INFORMATION

Regulatory Sponsor:	Sunnybrook Research Institute (SRI) 2075 Bayview Avenue Toronto, ON Canada M4N 3M5
Principal Investigator:	Dr. Angela Jerath
Academic Research Organization:	Centre for Clinical Trial Support, SRI 2075 Bayview Avenue Toronto, ON Canada M4N 3M5

2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice E6 (GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

Over 1.7 million hip and knee replacements are performed annually worldwide.[1,2] Hip and knee arthroplasty is associated with high blood loss (500-1500ml) and transfusion rates (18-22%).[3,4] High blood loss in this older patient group causes postoperative anemia that may need blood transfusion which is associated with adverse immune and non-immune reactions including fluid overload, lung injury, sepsis and incompatibility issues.[5,6]

Tranexamic acid (TXA) is a routinely used anti-fibrinolytic agent, which limits blood loss and transfusion requirements during joint replacement surgery. The routine use of TXA during surgery is recommended by the American Society of Orthopedic Surgeons, and the Hip and Knee Society.[7,8] Furthermore, a recent large meta-analysis, including 129 trials and 10488 patients, showed that TXA administration reduced the need for a transfusion by 38%, in a variety of surgery types.[9] However, there are currently no consensus guidelines regarding optimal TXA dosing for joint arthroplasty patients. Current TXA dosing practice is heterogeneous with most practitioners adopting regimens from trauma or previous clinical trials that use doses between 10-30 mg/kg.[10–12] However, these dosing regimens lack any supporting pharmacological evidence. In addition, TXA is cleared nearly 100% by glomerular filtration.[13] Evidence has shown that TXA accumulates in patients with chronic kidney disease (CKD) in proportion to the severity of renal dysfunction.[13–15] TXA dosing must be adjusted for patient renal function in order to avoid potentially toxic high plasma concentrations that could precipitate seizures and thrombosis.[15–19]

The main objective of this prospective observational study is to assess TXA blood concentrations in patients requiring major arthroplasty surgery with varied preoperative renal function. We will use this information to create new dosing guidelines for patients undergoing major arthroplasty surgery.

2.2 Clinical Data to Date

Optimal TXA dosing that maximizes the anti-fibrinolytic effect of TXA while avoiding toxic plasma concentration levels has been determined for cardiac surgery patients.[15] These studies built TXA pharmacokinetic (PK) models in patients with varying levels of renal dysfunction using population PK modeling, a powerful statistical method used by drug regulatory bodies to establish safe human dosing regimens.[20] This information was then used to develop new dosing regimens by

comparing PK data to older studies that showed plasma TXA levels around 100 mg/L provides near 100% anti-fibrinolytic activity.[15] Similar studies are absent for major joint replacement surgery. A separate study is required in this surgical population because of differences in fluid shifts and the lack of cardiopulmonary bypass.

2.3 Potential Risks/Benefits and Rationale

A total of 20 adult patients (>18 years of age) undergoing unilateral hip or knee replacement surgery will be included in this study. As all patients will be receiving standard of care treatment, we do not anticipate any additional risks to patients who participate in the study, beyond those normally associated with a surgery of this type. Only extra blood sampling will be required of a total volume of 30-50 ml.

3 STUDY OBJECTIVES

3.1 Primary Objective

Determine optimal TXA dose for patients undergoing hip and knee joint replacement surgery, with or without CKD.

3.2 Secondary Objective(s)

1. Develop a PK model and dosing regimen for major joint replacement surgery.

2. Study metabolomic profile of patients undergoing joint arthroplasty.

4 STUDY DESIGN

4.1 General Design

Our study follows a prospective cohort study design without randomization or blinding. 20 patients undergoing unilateral hip or knee replacement will be recruited and stratified into 2 groups (each with 10 patients) with either glomerular filtration rate (GFR) < 60 mL/min/1.73m2 (and dialysis) or GFR ≥ 60 mL/min/1.73m2. This GFR cut-off was chosen based on previous data showing low variability at GFR below and above 60, and plasma TXA levels differed due to reduction in TXA clearance rates between patients in each group.[15]

After spinal/regional or general anesthesia, a single intravenous bolus of 20 mg/kg TXA will be administered (as per our standard of care) over 15 minutes. Serial 4-5 ml blood samples will be drawn at: baseline/pre-TXA administration, 5 min, 15 min, 30 min, 1h, 1.5h, 3h, 6h+/-2 and 12h+/-4 post-bolus. These time points capture 2-3 TXA half-lives[14], including peak and end of surgery (average 2 h) concentrations.

Each blood sample will be collected into standard citrate collection tubes. Tubes will be inverted a minimum of 5 times to ensure proper mixing with anti-coagulant (sodium citrate). Each sample will be labeled with an anonymized patient study number (to de-identify patient information) and sample time. The tubes will be stored on ice bath following sample collection and then centrifuged within 2 hours at 2000g for about 15 min at 4˚C. The subsequent supernatant will be frozen and stored at -70˚C until analyzed. Measurement of TXA and other drug concentrations, renal biomarkers and metabolomics will be performed using liquid chromatography-tandem mass spectroscopy (LC-MS/MS) using previously described methodology.[15] Patients will otherwise receive routine perioperative care. Patient follow up will be to hospital discharge. Our approach is consistent with several previous studies in this area. [15,21]

All samples will be collected at SHSC (Holland Orthopaedic Arthritic Centre). Sample analysis and pharmacokinetic modeling will be performed at the Department of Pharmacology, University of Toronto. No external sponsors are affiliated with this study.

4.2 Primary Outcomes/Endpoint(s)

Our primary outcome is the measurement of serial plasma TXA concentrations in order to build PK models and dosing regimens for both patient groups. i.e. participants with GFR < 60 mL/min/1.73m2 (and dialysis) and participants with GFR ≥ 60 mL/min/1.73m2.

4.3 Secondary Outcomes/Endpoint(s)

We will report the following secondary outcomes:

1. Intraoperative blood loss and transfusion
2. % reduction in pre- and postoperative hemoglobin

3. Postoperative creatinine, GFR and other plasma renal biomarkers (e.g., NGAL, SUPAR, cystatin)
4. In-hospital mortality
5. Hospital length of stay

4.4 Primary Safety Outcomes/Endpoints

We do not anticipate any additional risks to participants associated with inclusion in this study. As such, no specific safety endpoints will be recorded.

5 PARTICIPANT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

Each participant must meet all of the following inclusion criteria to participate in this study:

1. Adults > 18 years of age
2. Elective unilateral hip or knee joint replacement

5.2 Exclusion Criteria

All participants meeting any of the following exclusion criteria at baseline will be excluded from participation in this study:

1. Contraindication to TXA (e.g., allergy, thrombophilia, tretinoin)
2. Advanced liver disease (>2-fold rise in liver enzymes, as this may alter PK analysis)
3. Anti-coagulant use within the last 1-4 days prior (depends on anticoagulant, prior to the day of surgery)

5.3 Participant Recruitment

Patients considered suitable for study selection will be identified by study research staff from local surgical populations and confirmed by study investigators. Prospective participants will then be informed and invited to participate in the research study by their clinical team (i.e. team member who is part of circle of care). Participants will be approached by study staff prior to their surgery in order to gain informed consent. Participants will be informed about the purpose, procedures, benefits, risks, discomforts, and any precautions related to the study. The participant will be given enough time to read and ask questions about the study. Participants will be considered enrolled in the study after granting informed consent.

No randomization or blinding procedures will be employed in this study, as all patients will receive the standard treatment. Patients will be stratified into two groups based on their GFR:

Group 1: GFR < 60 mL/min/1.73m^2

Group 2: GFR ≥ 60 mL/min/1.73m^2

5.4 Participant Withdrawal and Discontinuation of IP

5.4.1 Reasons for Withdrawal/Discontinuation of IP

Participants, or their substitute decision-maker, may withdraw from the study at any time and for any reason at their own discretion. Study participants may also be withdrawn from the study at the discretion of an investigator for reasons including, but not limited to patient safety.

5.4.2 Data Collection and Follow-up for Withdrawn Participants

In the event of patient withdrawal from the study, no further study procedures or evaluations will be performed or additional study data collected for that patient. Data collected prior to the withdrawal of consent will be included in the analysis. Every effort will be made to obtain permission to document the reason for withdrawal and to collect participant outcomes (e.g., survival data, any unresolved adverse events). Any relevant adverse events identified will be reported as per REB and Health Canada regulations.

6 INTERVENTIONS

6.1 Investigational Product

TXA is a routinely used, Health Canada approved, anti-fibrinolytic agent, frequently used to reduce blood loss during major surgery. The trial involves investigating the off-label use of TXA. A Health Canada approval ('No objection letter') will be obtained prior to initiating a trial.

6.1.1 Acquisition, Formulation and Packaging

6.1.1.1 Acquisition and Formulation

TXA is routinely administered to this patient population. We will be using our standard commercial stock (manufacturers SteriMax, Sandoz, Omega, Pfizer; as per institutional preference and directives as it will be used as part of clinical supply). The drug is stored at room temperature as a clear and colorless liquid. Standard concentration is 100 mg/ml.

6.1.1.2 Packaging

TXA is stored in glass vials. It is routinely kept in anesthesia drug carts. This drug is a standard of care for routine hip and knee replacement surgery, and thus is not an investigational product. This study aims to observe the plasma concentrations that our standard doses achieve.

6.1.2 Treatment Assignment Procedures

All consented study participants will be given the investigational product. Participants will be stratified to one of two groups based on kidney function/GFR.

6.1.3 Dosage, Preparation and Administration

Following administration of spinal/regional or general anesthesia, a single bolus dose of TXA (20 mg/kg) will be given intravenously to all study participants over 15 minutes, as per standard of care. See product monograph for detailed preparation and administration instructions.

6.1.4 Dose Modification

The dose used is a standard clinical dose administered to all patients without modification.

6.1.5 Receiving, Storage, Dispensing and Return

6.1.5.1 Receipt of Investigational Product

The investigational product (IP) is supplied by the hospital as per the institutional directives. Which IP is supplied is based on institutional preference as it will be used as part of clinical supply.

6.1.5.2 Storage and Stability

TXA should be stored at room temperature (15-30˚C) in the Pharmacy department.

6.1.5.3 Dispensing and Destruction of Investigational Product

The investigational product will be reconciled and destroyed by the pharmacy team as per the institutional directives.

6.1.6 Prior and Concomitant Medications/Treatments

We will collect the following preoperative information using medical history interview and medical record review:

- Aspirin
- Heparin
- LMWT heparin
- Plavix
- Other anti-platelet (clopidogrel)
- Other medications such as anti-hypertensives, diabetic medications.

7 STUDY SCHEDULE AND PROCEDURES

All research procedures and interventions will be conducted during the initial hospitalization involving the participant's surgery. Follow up will extend to hospital discharge.

7.1 Screening

Eligible participants will be identified by research personnel from existing hospital surgical populations and confirmed by study investigators according to previously described inclusion/exclusion criteria.

7.2 Baseline/Enrollment

Eligible individuals will be approached for informed consent prior to their surgery by appropriate research personnel. Individuals who give informed consent will be enrolled into the study. A baseline/pre-TXA blood sample will be taken prior to administration of the study intervention and used to stratify individuals into one of the two previously described groups according to their GFR.

7.3 Study visits

Following administration of the study intervention (i.e. 20 mg/kg TXA IV bolus), blood samples will be drawn after 5 min, 15 min, 30 min, 1h, 1.5h, 3h, 6h+/-2 and 12h+/-4 post-bolus. No additional patient interaction/study visits will be required.

Additional information relevant to the study will also be collected from patient medical records. This includes:

- Patient demographics
- Medical co-morbidities
- Medications
- Type and duration of surgery
- Blood transfusion/products
- Postoperative blood loss
- Laboratory tests (HB, PLT, Creatinine, INR, aPTT, eGFR)

7.4 Follow up

No follow ups requiring patient interaction will be required. Patient follow up will take the form of chart review only and extend only to the point of hospital discharge.

7.5 Protocol Deviations

It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this protocol are performed on study participants; the occurrence of deviations from the protocol or SOPs are limited; and compliance with the regulations is maintained. Planned

deviations from the protocol must not be implemented without prior agreement from the sponsor and approval from the local REB/ethics committee (EC), as required, unless to eliminate an immediate hazard to a participant.

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

8 ASSESSMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, and includes an adverse drug reaction (ADR).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or in significant disability/incapacity,
- Is a congenital abnormality or a birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Expected Serious Adverse Reactions according to the product monographs (SteriMax, Sandoz, Omega, Pfizer) include:

- Gastrointestinal disorders: gastrointestinal symptoms (nausea, vomiting, diarrhea) occur but disappear when the dose is reduced
- Nervous system disorders: dizziness, reduced blood pressure, seizures.
- Immune system disorders: allergic dermatitis, anaphylaxis or anaphylactoid reaction
- Eye disorders: impaired vision, blurred vision or colour vision impairment (chromatopsia)
- Vascular disorders: thromboembolic events (acute myocardial infarction, thrombosis, arterial thrombosis limb, carotid artery thrombosis, cerebral infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal

cortical necrosis, and central retinal artery and vein obstruction). Hypotension may occur after fast injection.

8.1.3 Unexpected Adverse Event

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the current Investigator's Brochure or Product Monograph.

8.1.4 Unexpected Adverse Drug Reaction (ADR)

An ADR is an adverse reaction, the severity of which is not consistent with the applicable Investigator's Brochure or Product Monograph. All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The expression "causal relationship" is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship. All serious and unexpected ADRs will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

8.2 Assessment of an Adverse Event

8.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the study drug (IP) caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the study drug, this should be clearly documented in the source documents.

8.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the Product Monograph (PM) or label.

8.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 8.1.2.

8.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms “serious” and “severe” are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3 Adverse Event Recording

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis.

Adverse Events that are determined by the Investigator to be definitely, probably, or possibly related to the study drug(s) will be recorded. Adverse events that are assessed and determined unrelated or unlikely related to the investigational product will not be recorded and reported.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency

- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of IP exposure

- Elective medical or surgical procedures.

8.4 Reporting of SAEs and Unanticipated Events

8.4.1 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

8.4.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting serious adverse events and serious and unexpected adverse drug reactions (SUADRs) to the sponsor in accordance with applicable regulations and reporting requirements and timelines.

Events that are assessed to be **serious and unexpected and related or cannot be ruled out as related** to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, a Suspect Adverse Reaction Report – CIOMS I Form must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

8.4.3 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

8.5 Type and Duration of Follow-up for Adverse Events

AEs occurring as of the first administered dose of the investigational product and until hospital discharge will be collected. AEs recorded during this period will be followed through to resolution, or until the event is assessed as chronic or stable.

8.6 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

Serious adverse event information will be entered into the CRF in a timely manner/**within 72 hours** from the time the investigator becomes aware of the event.

9 SITE MONITORING, AUDITING AND INSPECTING

9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the sponsor. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), Part C, Division 5 of the Food and Drug Regulations, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring is outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely. Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the site study team and the study QI. The institution and/or local REB reserves the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

9.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

Current TXA dosing procedures result in suboptimal plasma TXA concentrations.

10.2 Sample Size Considerations

Using a 2-tailed unpaired t-test with a significance α-level of 0.05, power of 80%, expected mean difference in TXA clearance of 0.0275 L/h/kg and standard deviation for all subjects of 0.044 L/h/kg (based on previous TXA studies in patients with different CKD stages) a total sample size of 20 patients (10 per group) is required.[13]

10.3 Planned Interim Analyses

No interim analyses will be performed.

10.4 Stopping Rules

This study will be stopped prior to its completion if:

a) The intervention is associated with adverse events that call into question the safety of the intervention.
b) Difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints.
c) Any new information becomes available during the trial that necessitates stopping the trial.

As per protocol section 7.3, following administration of the study intervention (i.e. 20 mg/kg TXA IV bolus), blood samples will be drawn after 5 min, 15 min, 30 min, 1h, 1.5h, 3h, 6h+/-2 and 12h+/-4 post-bolus. No additional patient interaction/study visits will be required, and we do not expect subjects to be withdrawn or replaced. The IP is being used in an observational study only as per standard hospital guidelines. If however, there is any adverse reaction to the IP, the standard internal hospital protocols will apply regrading monitoring the patient and treatment as appropriate to the reaction, plus notification of the adverse event.

10.5 Final Analysis Plan

10.5.1 PK modeling and development of dosing strategy

We will build 2 PK profiles for patients with GFR < 60 and with GFR ≥ 60 mL/min/1.73m2. We will determine clearance, volume of distribution, and inter-compartment rate constants using a 2-compartment model with mass balance equations.[15,21] NOMEM® 7.2.0 (non-linear mixed effects modeling, ICON Development Solutions, US) and ADAPT5 (D'Argenio, US) will be used for data fitting and population-PK analyses. Population-PK modeling will involve identification of

measurable source of variability and the relationship between PK and the pathological conditions (e.g. renal function), which are essential for dose optimization. Pathophysiological factors (e.g., body weight, creatinine clearance) that could explain the inter-subject variability will also be explored. The unexplained (random) variability in patient population will also be quantified.

The ratio of the steady state concentration to the therapeutic plasma concentration of 100 mg/L which provides near 100% inhibition of fibrinolytic activity, will be compared to guide the dose adjustment correction factor.

10.5.2 Statistics

Continuous variables will be summarized using median (interquartile range) and assessed using the Mann-Whitney U test. Categorical variables will be summarized using frequency (%) and assessed using a Chi-square test. These analyses will be performed using SAS v9.6 (US).

11 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. Where consent is required, each participant must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to:

- Worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- pharmacy dispensing records
- recorded data from automated instruments (i.e. ECGs)
- copies or transcriptions certified after verification as being accurate and complete
- participant files and records kept at the pharmacy
- entries entered directly into the printed CRF

We will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If

electronic source data documents is printed it should be signed and dated by the investigator to confirm content and filed with other source documents.

The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to participant medical records and will collect only the information needed for the study. Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

11.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range should be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

11.4 Data Capture

11.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Paper case report forms (pCRFs) will be used to collect data for this study. pCRFs are to be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices should be implemented according to standard operating procedures. All data requested on the pCRF must be recorded and verifiable by source documents.

11.5 Records Retention

It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents will be maintained in a secure and confidential manner for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period.

11.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the sponsor will be responsible for registering the study on Clinicaltrials.gov (*www.clinicaltrials.gov*), a publicly available registry that conforms to international standards for registries.

12 QUALITY CONTROL AND QUALITY ASSURANCE

As per ICH-GCP and local regulations, the sponsor is responsible for ensuring the implementation and maintenance of systems that support quality assurance and quality control.

The study must be conducted in compliance with the study protocol and all data collected must be accurate and verifiable by source document(s). For the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities, the site will provide direct access to all study related source data/documents. The sponsor will verify that the study is conducted and data has been collected, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Data for the study will be centrally stored and managed by the Centre for Clinical Trial Support (CCTS) at SHSC. To ensure the quality of study data, quality assurance and control systems will be implemented using validated electronic quality control checks within the electronic data capture system. These verification measures will identify missing data, inconsistencies and/or data anomalies. Both electronic and manual queries will be generated for resolution and review.

Access to secure and validated electronic systems used for the purposes of this study will be controlled by the sponsor. Access will only be granted to individual research team members upon review of training and qualification and authorization by delegation of the investigator.

Quality assurance and control measures will be implemented to ensure training for specific trial–related tasks beyond the usual scope of practice. Only procedures or interventions as outlined in Section 7, are considered study specific procedures requiring additional training, and will be reviewed for documentation of training and/or qualification.

13 ETHICS CONSIDERATIONS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6.

13.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

13.3 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A consent form describing in detail the study procedures and risks will be reviewed with and given to each participant. Consent forms will be REB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records.

Prior to involvement in any study-related activities, consent must be obtained in writing for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The ICF will be signed and dated by the participant and individual obtaining consent. The consent process will be documented in the clinical or research record.

The original ICF, in its entirety, will be maintained by the site, and a complete copy of the signed ICF provided to the participant. The rights and welfare of the participants will be protected by

emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The provision of consent is an ongoing process and should be maintained throughout the duration of the study. Participants may withdraw consent at any time throughout the course of the study.

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APPENDIX A: SCHEDULE OF EVENTS