Appendix 1. Examples of eligible surgeries associated with an RBC transfusion risk of ≥5%[12]

1. General surgery (esophagectomy, gastrectomy, gastric repair, small bowel repair or resection, ostomy formation, colon/rectum repair or resection, colostomy, splenectomy, hepatectomy, pancreatectomy, resection of abdominal mass)
2. Orthopedics (hip fracture repair, pelvic fixation, femur repair / fixation, shoulder / humerus open reduction internal fixation, lower extremity amputation)
3. Spine (vertebrectomy, surgery involving ≥ 3 levels)
4. Otolaryngology (glossectomy, mandibulectomy, radical laryngectomy)
5. Thoracic (lung resection or decortication)
6. Vascular (arterial bypass / endarterectomy / aneurysmorrhaphy involving the aorta or proximal vessels off the aorta)
7. Gynecology (hysterectomy)
8. Urology (nephrectomy, cystectomy, prostatectomy, pelvic exenteration)
9. Plastic surgery (large neoplasm resections, burns or debridements)
10. Surgeries anticipated to be associated with 5% or greater risk of RBC transfusion in hospital as per the surgical team.

Appendix 2. Summary of the patient priorities and perspectives from our patient partners that informed the altered consent model in the TRACTION Manitoba sites

Summary Of Patient And Caregiver Input And Feedback On Consent Model For The Traction Trial

Patients and caregivers of the Hematology & Critical Care Patient Partner Team have been involved in the design of the TRACTION trial for the last 18 months. At our meetings the topics discussed were the proposal, study purpose, study outcomes and more recently the study design and the model of consent. At our recent October meeting we discussed the differences between individual patient vs cluster control randomized clinical trials and the different models of consent suitable for those trial designs. We talked about the "traditional" informed consent, waived consent and our proposal of an "altered consent" or "altered waived consent".

We discussed the following advantages/disadvantages to various models of consent.

Traditional informed consent advantages

- Involving a "study drug", intervention, procedure or device with unknown short and long term side effects
- High/moderate risk interventions
- Most commonly used
- Knowledge of study is provided to patients before hand
- Ability for patients to opt-out
- Intended to protect the rights and welfare of participants

Traditional informed consent disadvantages

- May not be understandable
- Can be lengthy
- Many patients excluded
- The trial outcomes will still be applied to those excluded
- Patients in trials tend to have better outcomes
- Impractical (requires lots of resources, time and cost)
- Lower study enrollment numbers

Traditional waived consent advantages

- Involves well known, previously studied drugs, interventions, procedures or devices with known side effects
- Low risk interventions
- When informed consent is not practical; ie. Cluster randomized control trials
- Results are widely generalizable
- Risk adapted
- All patients studied

Traditional waived consent disadvantages

- Patients may not have prior knowledge of the study
- Individuals may not be given a choice to participate
- No opportunity to ask questions at any time
- Patients may not ever be informed that they were part of clinical research

Altered waived / Altered consent advantages

- Trial information provided to all patients – giving them the opportunity to ask questions
- Patients will have the ability to opt-out
- Greater protection of patient rights than a traditional waiver of consent (as patients will receive the trial information, ability to opt-out)

Altered waived / Altered consent disadvantages

- Communication may not reach all patients – but patients enrolled as emergent cases will be contacted by the coordinator and trial information will be provided with an opportunity to ask questions. These patients will also have the opportunity to opt-out and have their data removed from the trial database.
- No routine in-person discussion – but the study coordinators number is provided on the patient information brochure and is available to answer any questions.

The following are questions and responses we presented to the patient partner group.

1. In low-risk trials evaluating approved drugs, do you feel a different consent model such as “waived consent” can be appropriate in certain contexts?
   ☐Yes - 3
   ☐No - 2
   ☐Undecided
   ☐Other (specify): _____
2. Do you support a waived consent model for TRACTION?
   ☐Yes - 3
   ☐No - 2
   ☐Undecided
   ☐Other (specify): _____
3. Do you support an **altered** waived consent model for TRACTION?
   ☐Yes - 5
   ☐No
   ☐Undecided
   ☐Other (specify): _____
4. In an **altered** waived consent model, what would be your preferred method to receive information about the study? **Select all that apply.**
   ☐Study poster in pre-operative waiting and clinic rooms - 4
   ☐Patient brochure provided at pre-operative clinic appointment - 5
   ☐Study brochure attached to patient chart for patients to receive while in hospital - 2

☐Given the low-risk intervention (of which patients aren't routinely informed of at present), a patient information brochure isn't required
☐Other (specify):

Recommendation: *If emergent get info to patient in the mail*

5. Is there anything in the patient information poster / brochure that you would like to see changed (added or removed)?
☐Yes (specify): - 2

Recommendation: *Explain how it could benefit them and cost savings*
Recommendation: *Re work some of the language*

☐No - 3

Recommendation: *Sadly there are people who are anti-research. Brochures give these people information that they can respond to if so inclined.*

Additional notes:_____

_____

_____

6. Do you have any suggestions for different ways of communicating the trial to patients?
☐Yes (specify): - 1

Recommendation: *social media*

☐No - 4

7. In your opinion, is there a benefit to having a study website available for patients to access study information, progress, updates, and final results? Keeping in mind that study results could be years later.

☐Yes - 3
☐No -1
☐Other (specify): - 1

Recommendation: it may be difficult years later, engagement may be weakened

Additional notes: _____

_____

_____

_____

The outcome of the meeting was unanimous support from our patient partners for the use of the altered waived / altered consent model for the TRACTION trial. They also fully supported our strategy to disclose study information in the pre- anesthetic clinic by way of posters in the clinic waiting rooms and individual patient information

brochures. They aided in the development of the poster and patient information brochure and provided us with some valuable feedback on the design and information.

Appendix 3. TRACTION case report form

A. DEMOGRAPHICS:		
Month of Birth: ☐☐☐	Year of Birth: ☐☐☐☐	Estimated weight _____ kgs
Incision start date and Time: (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐ Time (24-hour clock): ☐☐:☐☐		
Cancer as primary indication for surgery? Yes ☐ No ☐		
Surgical procedure:		

B. ELIGIBILITY CONFIRMATION:	**YES**	**NO**
To the best of your knowledge, does the patient have any of the following exclusion criteria: a) Patient is <18 years of age b) Active thromboembolic disease **(within the last 3 months)** requiring anticoagulation c) Pregnancy d) Cardiac surgery and hip and knee arthroplasty where TXA is standard-of-care e) Surgeries with free flap reconstruction f) Trauma surgeries where TXA was administered within the previous 3 hours	☐	☐

C. STUDY DRUG INFORMATION:
100 mL = 1gr TXA or placebo; if patient weighs >100kg then 2gr = 2 mini-bags will be required as 1st dose

1st dose study drug assigned batch number: _____

☐ **Bolus _____ mL** **** to be completed within 10 minutes of incision, or as close to as possible.***

1st dose date and time administered

Date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐ Time (24-hour clock): ☐☐:☐☐

Was full volume given? ☐ Yes

☐ No Amount (mL): _____ Reason: _____

2nd dose study drug assigned batch number: _____

☐ **Bolus _____ mL** ☐ **Infusion _____mL**

2nd dose date and time administered

Date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐ Time (24-hour clock): ☐☐:☐☐

Was full volume given? ☐ Yes

☐ No Amount (mL): _____ Reason: _____

D. BLINDED EMERGENCY ALLOCATION -DRUG:	**YES**	**NO**
Was blinded emergency allocation drug administered? ***Blinded emergency allocation drug is only to be given if, despite administration of the second dose of study drug, it is felt to be absolutely required by the clinical team. If the patient received saline as the study drug, the emergency allocation drug will be TXA. However, if the patient received TXA as the study drug, the emergency allocation drug will be placebo.***	☐	☐

If used, emergency allocation drug assigned batch number:

☐ **Bolus _____ mL** ☐ **Infusion _____mL**

Date (dd/mmm/yyyy): ☐☐ / ☐☐☐ / ☐☐☐☐ Time (24-hour clock): ☐☐:☐☐

Was full volume given? ☐ Yes

☐ No Amount (mL): _____ Reason: _____

E. CONCOMITANT MEDICATIONS:	**Yes**	**No**
Anticoagulated for a condition other than Active Thromboembolic disease? **If yes:** ☐ **Venous thrombosis** ☐ **Arterial thrombosis** ☐ ***Atrial fibrillation*** ☐ **Other:** _____	☐	☐
Topical TXA	☐	☐
Cell saver (returned to patient)	☐	☐
Intraoperative DVT prophylaxis *If yes,* ☐ the beginning of the case ☐ during the case ☐ at the end of the case	☐	☐

F. ADVERSE EVENTS: *please select all that apply*	
Seizures	☐
Anaphylaxis	☐

G. Off-protocol use of tranexamic acid	
Dose: _____ mg	Time (24-hour clock): ☐☐:☐☐

Comments:_____

_____

Attending anesthesiologist or designate

Name: _____ **Signature:** _____

Appendix 4. List of diagnostic, physician billing and imaging codes for venous thromboembolism outcome.

ICD_10_DVT	ICD-10-CA: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1
ICD_10_PE	ICD-10-CA: I26.9, I26.0
OHIP_DVT	J198, J498, J193, J493, J202, J502, J659, J660
OHIP_PE	J859, J860, X406, X407, X125
CCI_DVT	3KX30DA, 3KX30DB, 3KX30DC, 3KX30DD, 3KR10VA, 3KR10VC, 3KR10VN, 3KR12VA, 3KX10VA, 3KX10VC, 3KX10VN, 3KX10VX, 3KX12VA
CCI_PE	3IM10VC, 3IM10VX, 3IM10VY, 3IM12VA, 3GT70CA, 3GT70CC, 3GT70CE, 3GT70KC, 3GT70KD, 3GT70KE, 3JY10VA, 3JY10VC, 3JY10VN, 3JY10VX, 3JY12VA, 3JY20WC, 3JY20WE, 3GT20WC, 3GT20WE

ICD_10 = International Classification of Diseases, Tenth Revision; OHIP = Ontario Health Insurance Plan; CCI = Canadian Classification of Health Interventions; DVT = deep vein thrombosis; PE = pulmonary embolism

Appendix 5. Statistical analysis plan

Statistical Analysis Plan for a Phase IV randomised controlled trial of a hospital policy of Tranexamic acid to reduce transfusion in major non-cardiac surgery (TRACTION)

SAP Version Number	*Version 1.0 (19/06/2023)*
Protocol Version and Date	*Version 5.0 (20/10/2021)*
Trial Statistician	*Tim Ramsay*
Senior Statistician	*Robert Balshaw*
Trial Chief Investigator	*Ryan Zarychanski / Dean Fergusson*
SAP Authors	*Brett Houston, Tim Ramsay, Robert Balshaw, Dan McIsaac, Rodney Breau, Dean Fergusson, Ryan Zarychanski*

Revision Control

Protocol Version	Updated SAP version number	Section number changed	Description of change	Date changed

SAP Signatures

SAP Version Number being approved: 1.0

I give my approval for the attached SAP entitled TRACTION dated June 19, 2023.

Trial Statistician

Name:

Signature: _____

Date: _____

Senior Statistician

Name:

Signature: _____

Date: _____

Chief Investigator

Name:

Signature: _____

Date: _____

Chief Investigator

Name:

Signature: _____

Date: _____

Roles and responsibilities

Name	Role	Institution
Tim Ramsay	*Trial Statistician*	*OHRI - Ottawa Methods Centre*
Robert Balshaw	*Senior Statistician*	*University of Manitoba*
Ryan Zarychanski	*Chief Trial Investigator/Sponsor*	*University of Manitoba*
Dean Fergusson	*Chief Trial Investigator*	*OHRI – Ottawa Methods Centre*
Brett Houston	*Trial Investigator*	*University of Manitoba*
Rodney Breau	*Trial Investigator*	*OHRI- Ottawa Hospital Research Institute*
Daniel McIsaac	*Trial Investigator*	*OHRI- Ottawa Hospital Research Institute*

Contributions

Tim Ramsay and Robert Balshaw developed the statistical analysis plan (SAP) based on the outlined analyses set out in the trial protocol. Brett Houston, Ryan Zarychanski, Dean Fergusson, Tim Ramsay, Daniel McIsaac, Rodney Breau contributed content and approved the SAP.

Abbreviations and Definitions

CAC	Cluster autocorrelation
DAH	Days at home
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
ICC	Intraclass correlation
ICU	Intensive care unit
ITT	Intention to treat
IV	Intravenous
LOS	Length of stay
OHRI	Ottawa Hospital Research Institute
PE	Pulmonary embolus
QI/PI	Qualified investigator/Principal investigator
RBC	Red blood cells
REB	Research ethics board
RC	Research coordinator
RCT	Randomized control trial
SAP	Statistical Analysis Plan
TXA	Tranexamic acid
VTE	Venous thromboembolism

Section 1: Introduction

This is the statistical analysis plan (SAP) that dictates the analysis of the TRACTION trial, a Phase IV trial of a hospital policy of tranexamic acid to reduce transfusion in major non-cardiac surgery.

This plan has been prespecified by the investigators who are all blinded to trial data other than recruitment statistics and reported adverse events.

At the time this SAP was conceived and finalized, enrollment is ongoing and is expected to be completed by approximately March 2024.

Houston BL, *et al. BMJ Open* 2024; 14:e084847. doi: 10.1136/bmjopen-2024-084847

Section 2: Trial Summary

Background and Rationale

Perioperative bleeding is a major indication for red blood cell (RBC) transfusion and the second most common reason for transfusion among hospitalized patients[1,2]. Approximately 50% of patients undergoing major cardiac and revision orthopedic surgery require RBC transfusions[3,4]. The rates of transfusion in other major, and more commonly performed, non-cardiac surgeries can approach or exceed these estimates[5]. RBC transfusions are a scarce and costly resource associated with adverse patient outcomes[6,7]. Tranexamic acid (TXA) is an inexpensive (~$5-10 per surgery) and widely available drug given during surgery reduces RBC transfusion in cardiac surgery and hip and knee arthroplasty[8]. However, due to the lack of high-quality evidence, the clinical effectiveness and safety of TXA in other major surgeries with comparable transfusion rates is uncertain. Demonstrating that TXA can safely reduce transfusion in a broad patient population undergoing major non-cardiac surgery will forward a new standard of care, reduce costs, and promote the sustainability of Canada's blood supply.

Objectives

Overall hypothesis: We hypothesize that hospital-level implementation of routine tranexamic acid use in patients undergoing major non-cardiac surgery will reduce RBC transfusion without increasing thrombotic risk.

Section 3: Study Methods

3.1 Trial Design

TRACTION is a pragmatic, multi-centre, blinded registry-based cluster crossover randomized controlled trial.

Intervention: **Tranexamic acid.** TXA 1 gram bolus (2 grams for patients over 100 kg) intravenously (IV) administered within 10 minutes of the first surgical incision, followed by 1 additional gram given intravenously prior to skin closure, at the discretion of the anaesthesiologist (e.g., IV bolus at 2-4 hours of surgery, at skin closure, or as a continuous infusion throughout the surgical procedure).

Control: **Placebo**. Matching placebo bolus and/or infusion.

Blinding: To minimize sources of selection and ascertainment biases, anaesthesiologists, surgeons, investigators, research staff, and members of the Data Safety and Monitoring Board will all be blinded to randomization schemes and treatments administered; only the trial statistician will have access to randomization schemes for all sites. The research site's Pharmacy staff will not have contact with the study team or the patient and will be expressly forbidden to discuss individual treatment allocation with the study team, the patient, the operating room or the clinical care teams unless emergency unblinding is warranted. Clinical teams will be permitted to unmask treatment allocation only under exceptional circumstances.

3.2 Eligibility

Patients ≥ 18 years of age undergoing major noncardiac surgery, defined as an inpatient surgery with an estimated ≥ 5% risk of RBC transfusion, including open surgeries or laparoscopic surgeries with an estimated duration of ≥ 3 hours.

Examples of eligible surgeries could include (but are not limited to):

1. General surgery (esophagectomy, gastrectomy, gastric repair, small bowel repair or resection, ostomy formation, colon/rectum repair or resection, colostomy, splenectomy, hepatectomy, pancreatectomy, resection of abdominal mass)
2. Orthopedics (hip fracture repair, pelvic fixation, femur repair / fixation, shoulder / humerus open reduction internal fixation, lower extremity amputation)
3. Spine (vertebrectomy, surgery involving ≥ 3 levels)
4. Otolaryngology (glossectomy, mandibulectomy, radical laryngectomy)
5. Thoracic (lung resection or decortication)

6. Vascular (arterial bypass / endarterectomy / aneurysmorrhaphy involving the aorta or proximal vessels off the aorta)
7. Gynecology (hysterectomy)
8. Urology (nephrectomy, cystectomy, prostatectomy, pelvic exenteration)
9. Plastic surgery (large neoplasm resections, burns or debridements)
10. Surgeries anticipated to be associated with 5% or greater risk of RBC transfusion in hospital as per the surgical team.

3.3 Randomization

Over the duration of the study, participating centres will be centrally and randomly allocated within site-pairs, one site to receive either TXA and the other to receive placebo at 4-week intervals for a minimum of 8 months per site. Within each pair of sites, 4-week periods will be randomized so that the two sites always have opposite treatments. The randomization will be in permuted blocks of size 2 and 4 applied to the first site in the pair, with the second site receiving the opposite treatment.
Sites will be paired by the principal investigator based on surgical volume, surgical specialization and data processes. Intervention assignment will only be known to the research pharmacy staff who will prepare the study drug specific to the interval assignment.

3.4 Sample Size

The TRACTION trial has been designed with two co-primary outcomes that incorporate clinical effectiveness and safety. The total sample size of 8320 patients reflects the power needed to inform the safety outcome of venous thromboembolism (VTE).

1. Transfusion (effectiveness; superiority): Informed by our large observational study, the average cluster-period size is predicted to be 130 patients. Estimating a within-period intraclass correlation (ICC) of 0.005 and a cluster autocorrelation (CAC) of 0.85 in the TRACTION trial, with a minimum of 8 clusters randomly assigned to a minimum of 8 monthly study intervals, we will have 99.9% power to detect an 6% absolute risk difference in the proportion of patients transfused RBCs from a baseline transfusion rate of 18%.
2. VTE (safety; non-inferiority): Informed by previously published estimates of DVT and PE following major surgery where TXA had been used, with an average cluster period size of 130 patients, an ICC of 0.005 and a CAC of 0.85, in a minimum of 8 clusters randomly assigned to a minimum of 8 monthly study intervals, we will have 83% power to exclude a 1% or greater increase in VTE at 3 months from a predicted baseline rate of 2.2%. As study analyses require direct calculation of intervention effects on a relative (ie, odds ratio) scale, this absolute risk difference will be converted to inform our non-inferiority margin of

1.47 (specifically, if the upper bound of the one-sided 97.5% CI of the odds ratio excludes 1.47, we will conclude non-inferiority).

Placing effectiveness in the context of safety, TRACTION will be overpowered to evaluate the superiority of our co-primary transfusion effectiveness outcome, but adequately powered to detect a clinically relevant increase in thrombosis.

3.5 Interim analyses and stopping guidance

Given the short enrolment period (minimum of 8 months per site), low rates of VTE reported in published trials, and need for 90 day follow-up for rates of VTE to mature, no formal interim analyses are planned. While effectiveness could be ascertained after 50% of patients are enrolled, even if TXA were found to be superior to placebo after enrolment of 50% of patients, a complete clinical decision to adopt a policy of TXA could not be made until the rate of VTE is known for all patients enrolled.

3.6 Trial status at the time of SAP preparation

Enrolment in the TRACTION trial began 16/Feb/2022 at the Health Sciences Centre and St Boniface Hospital sites. Hospitals (cluster units) were added in pairs based on regulatory approvals and site readiness. All 10 hospital cluster units (5 pairs) were enrolling patient as of 26/Mar/2023, as site start-up was delayed due to COVID. Completion of enrolment is anticipated to be the first quarter of 2024.

3.7 Timing of final analysis

The trial will close when the last 90 day follow-up assessment is completed (anticipated to occur at the end of May 2024). The data will then be cleaned, verified, and locked. Analysis will commence once the final lock has been confirmed by the principal investigator.

3.8 Definition and Timing of Trial Outcomes

The following endpoints will be analyzed, displayed graphically, and summarized with descriptive statistics.

Primary outcomes:

1. Proportion of patients transfused RBCs

- Dichotomous outcome of patient who received a transfusion of 1 or more RBC units
- Timing: Assessment period is from one hour prior to surgery start to end of index hospital admission (discharge or death), censored at 90 days
- Ascertainment: Hospital electronic clinical transfusion databases

2. Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE)
    - Dichotomous outcome of a diagnosis of deep vein thrombosis or pulmonary embolism
    - Timing: Assessment period is from surgery start to 90 days postoperative
    - Ascertainment: Provincial administrative databases using a combination of physician billing and imaging codes

Secondary outcomes:

Transfusion

3. Number of RBC units transfused (both at cluster level and patient level)
    - Continuous outcome indicating the number of RBC units transfused
    - Timing: Assessment period is from one hour prior to surgery start to the end of index hospital admission (discharge or death)
    - Ascertainment: Hospital electronic clinical transfusion databases

Safety

4. Myocardial infarction
    - Dichotomous outcome of diagnosis of myocardial infarction
    - Timing: Assessment period is from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Discharge abstract database

5. Stroke (Ischemic)
    - Dichotomous outcome of diagnosis of ischemic stroke
    - Timing: Assessment period is from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Discharge abstract database

6. Deep vein thrombosis
    - Dichotomous outcome of diagnosis of deep vein thrombosis
    - Timing: Assessment period is from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Provincial administrative databases using a combination of diagnostic, physician billing and diagnostic imaging codes

7. Pulmonary embolism
    - Dichotomous outcome of diagnosis of pulmonary embolus

- Timing: Assessment period is from time of index hospital admission to end of index hospital admission (discharge or death)
- Ascertainment: Provincial administrative databases using a combination of physician billing and imaging codes

Clinical

8. Hospital length of stay (LOS)
    - Continuous outcome indicating the duration of hospital length of stay in days
    - Timing: Assessed from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Discharge abstract database

9. Intensive care unit (ICU) admission
    - Dichotomous outcome reflecting progression of critical illness requiring admission to an intensive care unit
    - Timing: Assessed from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Discharge abstract database

10. Hospital survival
    - Dichotomous outcome of survival
    - Timing: Assessed from time of index hospital admission to end of index hospital admission (discharge or death)
    - Ascertainment: Discharge abstract database

11. Overall survival
    - Dichotomous outcome of survival
    - Timing: Assessed from time of index hospital admission to 90 days postoperative
    - Ascertainment: Provincial administrative databases

12. Number of days alive and out of hospital to day 30
    - Continuous outcome indicating the number of days a patient is alive and out of an acute care hospital
    - Timing: Assessment period from time of index hospital admission to 30 days postoperative
    - Ascertainment: Discharge abstract database

Compliance

13. Policy compliance in enrolled patients
    - Dichotomous outcome reflecting the proportion of enrolled patients who received a minimum of one dose of the study intervention
    - Timing: Assessed intraoperatively

- Ascertainment: Trial case report form

3.9 Baseline Patient Characteristics

The following demographics will be summarized across arms: age, sex, weight, Charlson comorbidity index, surgical urgency (elective vs. urgent/emergent), surgery type (general surgery, orthopaedic surgery, spine surgery, otolaryngology, thoracic surgery, vascular surgery, gynaecologic surgery, urologic surgery, plastic surgery), surgical approach (open versus endoscopic), oncologic surgery, preoperative RBC transfusion, preoperative haemoglobin, preoperative platelet count, preoperative creatinine, and preoperative INR. More may be added as baseline summaries.

Section 4: Statistical Principles

4.1 Confidence Intervals and P-values

The co-primary outcomes will be analysed without adjustment for multiplicity as both hypothesis tests must be statistically significant (i.e., superior for reducing RBC transfusion and non-inferiority for VTE) before the intervention will be concluded to be beneficial. The odds ratio for transfusion between the two arms will be tested at a 0.05 level of significance. The odds ratio for VTE between the two intervention arms will be tested using a one-sided confidence interval at the 0.025 level of significance according to standard non-inferiority testing practice.

4.2 Adherence and protocol deviations

Methods to mitigate emergency unblinding in the cluster trial: Regardless of cluster treatment assignment, off-protocol and unblinded TXA can be administered by the anaesthesiologist if they or the surgeon feel it's absolutely required. In the exceptional circumstance the clinical team requires confirmation of tranexamic administration (i.e., excessive intraoperative bleeding/haemorrhage), blinded emergency investigational product will be available upon request. The emergency investigational product will contain either placebo or tranexamic acid, contingent on whether the hospital is randomized to tranexamic acid or placebo, respectively. This ensures that all patients receive tranexamic acid without inadvertent over- or underdosing. Given the cluster trial design, this also negates the need for emergency unblinding which could compromise the site for the randomization period.

We will assess adherence by evaluating policy compliance in enrolled patients.

4.3 Analysis populations

Intention to treat (ITT) population: all subjects who were randomized.

Per-protocol (PP) population: all patients except those who were allocated to receive TXA who did not receive 1 or more doses of TXA or those allocated to placebo who received TXA.

4.4 Period

Period will be coded as an integer beginning at 1 for the first 4-week period. Note that if centres do not all begin at the same time then not all centres will start period at time 1. However, each centre's period will be consecutive from the first period that centre

began randomizing and each period will contain at least two centres with opposite treatment allocation.

Section 5 – Analysis

5.1 Analysis Methods

Co-Primary Hypotheses:

H1: The proportion of participants transfused RBCs is lower in those assigned to receive TXA than in those assigned to receive placebo (i.e., leading to a superiority analysis using the ITT analysis set).

H2: The proportion of patients experiencing VTE within 90 days of surgery will be no worse in those who received TXA compared to those assigned to receive placebo (i.e., leading to a non-inferiority analysis in both the ITT and PP analysis sets).

Because the trial will be considered successful only if both null hypotheses are rejected, we will test H1 at the 0.05 level and H2 at the 0.025 level.

Primary Analyses

H1: Superiority of TXA

We will test for the superiority of TXA in terms of RBC transfusion by examining the p-value for the odds ratio (OR) for the occurrence of RBC transfusion in the TXA group using the ITT analysis set. The OR will be estimated from a mixed-effects logistic regression model with centre included as a random effect, using PROC GLIMMIX in SAS. Since mixed effects logistic models often fail to converge, we specify a hierarchy of four models defined as follows.

Our final analysis will be based on the first of these to converge. The first model uses a robust variance estimator with the Mancl and DeRouen correction to the standard error.

```
PROC GLIMMIX DATA=indiv NOCLPRINT EMPIRICAL=FIRORES ;
CLASS cluster period (REF=FIRST) ;
MODEL outcome(EVENT='1') = trt period / DIST=BINARY LINK=LOGIT
SOLUTION DF=8;
RANDOM cluster;
ESTIMATE 'intervention' trt 1 / CL EXP ;
RUN ;
```

If the first model does not converge, we will resort to the second model which uses a robust variance estimator without the Mancl/DeRouen correction and specified an autoregressive error structure.

```
PROC GLIMMIX DATA=indiv NOCLPRINT METHOD=QUAD;
 CLASS cluster period (REF=FIRST) ;
MODEL outcome(EVENT='1') = trt period / DIST=BINARY LINK=LOGIT
SOLUTION DF=8;
RANDOM period / SUBJECT=cluster TYPE=AR(1);
ESTIMATE 'intervention' trt 1 / CL EXP ;
RUN ;
```

The third model option uses a simpler covariance structure.

```
PROC GLIMMIX DATA=indiv NOCLPRINT METHOD=QUAD;
CLASS cluster period (REF=FIRST) ;
MODEL outcome(EVENT='1') = trt period / DIST=BINARY LINK=LOGIT
SOLUTION DF=8;
RANDOM period/SUBJECT=cluster TYPE=VC;
ESTIMATE 'intervention' trt 1 / CL EXP ;
RUN ;
```

The final option specifies a random intercept for each centre (cluster) but does not otherwise account for between-period intra-cluster correlation.

```
PROC GLIMMIX DATA=indiv NOCLPRINT METHOD=QUAD;
CLASS cluster period (REF=FIRST) ;
MODEL outcome(EVENT='1') = trt period / DIST=BINARY LINK=LOGIT
SOLUTION DF=8;
RANDOM intercept / SUBJECT=cluster;
ESTIMATE 'intervention' trt 1 / CL EXP ;
RUN ;
```

The null hypothesis will be rejected in favour of superiority of TXA if the treatment odds ratio is statistically significant and less than one.

H2: Non-inferiority of TXA

We will test the non-inferiority of TXA in terms of VTE by examining the one-sided 97.5% confidence interval for the OR of the occurrence of VTE using the same model as used for H1.

The null hypothesis will be rejected in favour of non-inferiority of TXA at the 0.025 level if the upper endpoint of the one-sided 97.5% confidence interval for the OR is below 1.47.

Missing Data
As the primary and secondary endpoints are based on routinely collected variables, negligible missing observations are anticipated. However, in the case that a primary or secondary endpoint is not available for a participant a complete case analysis will be performed.

Analysis of secondary outcomes:
The absolute differences in the dichotomous secondary outcomes (in-hospital diagnosis of myocardial infarction, stroke, DVT or PE and need for ICU admission) will be analysed as described for the primary effectiveness outcome above. The continuous secondary outcome (number of RBC units transfused) will be analysed using linear regression analysis. Number of days alive and out of hospital to day 30 will be analysed using negative binomial regression analysis. Hospital length of stay, hospital survival and 90 day survival will be analysed using Cox proportional hazards regression analysis. The assumption of proportional hazards will be assessed using Schoenfeld residuals. Results will be expressed as hazard ratios with 95% confidence intervals. Consistent with our primary outcomes, analysis of all secondary outcomes will be unadjusted, although sensitivity analyses will be performed adjusting for age, sex, surgery type, surgical urgency, and preoperative haemoglobin concentration.

Subgroup and secondary analyses:
Effect modification for both co-primary outcomes will be investigated through the use of interaction terms within the main model. Candidate effect modifiers include age, surgery type, surgical urgency, transfusion risk, and cancer status.

5.2 Harms

TXA is not known to be associated with adverse events when used in non-cardiac surgery. In cardiac surgery, rare events of seizure activity have been described up re-emergence from anaesthesia. Though not expected, incidence of perioperative seizure activity or immediate allergic reaction to the study drug will be ascertained and reported. Serious adverse events will constitute seizure activity or allergic reactions that result in death, are life-threatening, prolong hospitalization, cause significant disability or incapacity, or cause another condition judged as serious. Serious adverse events will be reported to the coordinating centre within 24 hours.

The occurrence of VTE at 90 days is our primary safety outcome and a co-primary outcome for the TRACTION trial. This outcome will be ascertained at the end of the trial using administrative billing, prescribing and physician reimbursement data and radiology

reports. The TRACTION trial is a minimal risk registry-based trial - in over 50,000 patients randomized to receive TXA or placebo in trauma, post-partum haemorrhage, head injury, cardiac surgery, or non-cardiac surgery, there was no evidence of increased thrombosis or other events to suggest increased harm.

Section 6 – List of Pre-Specified Analyses

Prospectively defined primary, secondary, sensitivity and safety analyses are summarized in **Table 1**.

Table 1. Primary, sensitivity, secondary, safety, and per protocol analyses

#	Status	Analysis Set	Outcome	Notes
7.1	Primary analysis Co-Primary Effectiveness	Intention to treat	Proportion transfused RBCs	Dichotomous
7.2	Primary analysis Co-Primary Safety	Per protocol	VTE (DVT or PE)	Dichotomous
7.3	Subgroup Co-Primary Effectiveness	Intention to treat	Proportion transfused RBCs	Effect modification by subgroup of age, surgical type, surgical urgency, transfusion risk, and cancer status
7.4	Subgroup Co-Primary Safety	Per protocol	VTE (DVT or PE)	Effect modification by subgroup of age, surgical type, surgical urgency, transfusion risk, and cancer status
7.5	Sensitivity Co-Primary Effectiveness	Intention to treat	Proportion transfused RBCs	With baseline covariable adjustment*
7.6	Sensitivity Co-Primary Safety	Per protocol	VTE (DVT or PE)	With baseline covariable adjustment*
7.7	Secondary - transfusion	Intention to treat	Number of RBC units transfused – day 3	Continuous
7.8	Secondary - transfusion	Intention to treat	Number of RBC units transfused – day 7	Continuous
7.9	Secondary - transfusion	Intention to treat	Number of RBC units transfused – to end of index hospitalization	Continuous
7.10	Secondary – safety	Intention to treat	Myocardial infarction	Dichotomous
7.11	Secondary – safety	Intention to treat	Ischaemic stroke	Dichotomous
7.12	Secondary – safety	Intention to treat	Deep vein thrombosis	Dichotomous
7.13	Secondary – safety	Intention to treat	Pulmonary embolism	Dichotomous
7.14	Secondary – clinical	Intention to treat	ICU admission	Dichotomous
7.15	Secondary – clinical	Intention to treat	Hospital LOS	Continuous
7.16	Secondary – clinical	Intention to treat	Hospital survival	Dichotomous
7.17	Secondary – clinical	Intention to treat	Overall survival	Dichotomous
7.18	Secondary – clinical	Intention to treat	Number of days alive and out of hospital to day 30	Continuous
7.19	Secondary – compliance	Intention to treat	Proportion of patients receiving ≥1 dose of the study intervention	Dichotomous
7.20	Sensitivity Secondary - transfusion	Intention to treat	Number of RBC units transfused – day 3	With baseline covariable adjustment*
7.21	Sensitivity Secondary - transfusion	Intention to treat	Number of RBC units transfused – day 7	With baseline covariable adjustment*
7.22	Sensitivity Secondary - transfusion	Intention to treat	Number of RBC units transfused – to end of index hospitalization	With baseline covariable adjustment*

7.23	Sensitivity Secondary – safety	Intention to treat	Myocardial infarction	With baseline covariable adjustment*
7.24	Sensitivity Secondary – safety	Intention to treat	Ischaemic stroke	With baseline covariable adjustment*
7.25	Sensitivity Secondary – safety	Intention to treat	Deep vein thrombosis	With baseline covariable adjustment*
7.26	Sensitivity Secondary – safety	Intention to treat	Pulmonary embolism	With baseline covariable adjustment*
7.27	Sensitivity Secondary – clinical	Intention to treat	ICU admission	With baseline covariable adjustment*
7.28	Sensitivity Secondary – clinical	Intention to treat	Hospital LOS	With baseline covariable adjustment*
7.29	Sensitivity Secondary – clinical	Intention to treat	Hospital survival	With baseline covariable adjustment*
7.30	Sensitivity Secondary – clinical	Intention to treat	Overall survival	With baseline covariable adjustment*
7.31	Sensitivity Secondary – clinical	Intention to treat	Number of days alive and out of hospital to day 30	With baseline covariable adjustment*
7.32	Sensitivity Secondary – compliance	Intention to treat	Proportion of patients receiving ≥1 dose of the study intervention	With baseline covariable adjustment*

* Baseline covariables to include: age, sex, surgery type, surgical urgency, and preoperative haemoglobin concentration. Age will be categorized as <40, 40-64, 65-74 and ≥ 75 years. Sex will be dichotomous. Surgery type will be categorized by surgical specialty into general surgery, orthopaedic surgery, spine surgery, otolaryngology, thoracic surgery, vascular surgery, gynaecologic surgery, urologic surgery, and plastic surgery. Surgical urgency will be categorized as elective vs. urgent/emergent. Preoperative haemoglobin will be categorized according to WHO severity categories.

Appendix 6. Ontario and Manitoba provincial and site-level institutional approvals, as applicable.

Ontario Sites:

The following sites fall under Clinical Trial Ontario's Provincial approval (CTO Project ID: 2028) and do not require site-specific ethics approvals:

- Health Sciences North Research Institute
- Kingston Health Sciences Centre
- Hôpital Montfort

The following Ontario sites have site-specific approvals in addition to the CTO provincial approval:

- London Health Sciences Centre: Approved by the Lawson Health Research Institute (Study ID: R-23-061)
- Humber River: No study-specific number is assigned
- Ottawa Hospital General site
- Ottawa Hospital Civic site
    - Note: The Ottawa Hospital General and Civic site approvals utilize the same study number as the CTO provincial regulatory body

Manitoba Sites:

- Biomedical Research Ethics Board (Provincial): HS23176 (B2019:096)
- Health Sciences Centre: RI2020:153
- St. Boniface Hospital: RRC/2020/1911
- Grace Hospital: No study-specific number is assigned