

# BMJ Open Tranexamic acid versus placebo to reduce perioperative blood transfusion in patients undergoing liver resection: protocol for the haemorrhage during liver resection tranexamic acid (HeLiX) randomised controlled trial

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## ABSTRACT

**Introduction** Despite use of operative and non-operative interventions to reduce blood loss during liver resection, 20%–40% of patients receive a perioperative blood transfusion. Extensive intraoperative blood loss is a major risk factor for postoperative morbidity and mortality and receipt of blood transfusion is associated with serious risks including an association with long-term cancer recurrence and overall survival. In addition, blood products are scarce and associated with appreciable expense; decreasing blood transfusion requirements would therefore have health system benefits. Tranexamic acid (TXA), an antifibrinolytic, has been shown to reduce the probability of receiving a blood transfusion by one-third for patients undergoing cardiac or orthopaedic surgery. However, its applicability in liver resection has not been widely researched.

**Methods and analysis** This protocol describes a prospective, blinded, randomised controlled trial being conducted at 10 sites in Canada and 1 in the USA. 1230 eligible and consenting participants will be randomised to one of two parallel groups: experimental (2 g of intravenous TXA) or placebo (saline) administered intraoperatively. The primary endpoint is receipt of blood transfusion within 7 days of surgery. Secondary outcomes include blood loss, postoperative complications, quality of life and 5-year disease-free and overall survival.

**Ethics and dissemination** This trial has been approved by the research ethics boards at participating centres and Health Canada (parent control number 177992) and is currently enrolling participants. All participants will provide written informed consent. Results will be distributed widely through local and international meetings, presentation, publication and ClinicalTrials.gov.

**Trial registration number** NCT02261415.

## Strengths and limitations of this study

- This is the largest multicentre and internationally registered randomised, placebo-controlled and blinded trial investigating the effects of tranexamic acid (TXA) in liver resection surgeries.
- Pragmatic design with minimal intervention and broad eligibility criteria allow for practicality and high external validity.
- The study included quality-of-life evaluations, disease recurrence and overall survival for 5 years after surgery to determine the long-term outcomes of using TXA in liver resections.
- Lack of standardisation in anaesthesia and surgical technique may yield important variability.
- Improvement in blood management practices over time and inclusion of patients at low risk of blood transfusion may reduce the baseline transfusion rate, resulting in insufficient power to detect differences.

## INTRODUCTION

### Background and rationale

Liver resection is the preferred treatment for patients with primary or metastatic liver malignancies, benign liver tumours and some biliary diseases.<sup>1–5</sup> In Canada, over 2000 patients annually undergo liver resection, predominantly for cancer.<sup>6</sup> Despite improvements such as advances in preoperative imaging and evaluation of liver functional reserve, liver resection remains a major

undertaking, with a 90-day postoperative mortality of approximately 10%.<sup>7–9</sup>

### Blood loss and conservation

There are several operative and non-operative interventions to reduce blood loss during liver resection. Operatively, surgeons may use sophisticated methods of liver dissection and parenchymal transection, including ultrasonic dissectors, hydrodissectors, bipolar cautery and stapling devices.<sup>10–12</sup> Surgeons may selectively reduce the blood flow to the liver during liver resection by continuously or intermittently clamping the portal vein and hepatic artery (the Pringle manoeuvre).<sup>10</sup> The anaesthesiologist has a crucial role in reducing blood loss and transfusion requirements by maintaining a low central venous pressure (CVP) during parenchymal transection.<sup>13</sup> These advances have resulted in substantially less blood loss during liver surgery compared with prior decades. Nevertheless, bleeding remains a problem during major liver resection, with 20%–40% of patients receiving perioperative blood transfusions in large series.<sup>7 14 15</sup>

Extensive intraoperative blood loss is a major risk factor for postoperative morbidity and mortality.<sup>16–22</sup> Blood transfusion itself carries serious risks, including transfusion-transmitted viruses, transfusion-related acute lung injury, transfusion-associated circulatory overload, acute haemolytic transfusion reactions, bacterial contamination and severe allergic reactions.<sup>23 24</sup> Furthermore, intraoperative blood loss and perioperative blood transfusion are strongly associated with long-term cancer recurrence and overall survival independent of perioperative adverse events, possibly through host immunosuppression caused by allogenic blood transfusion.<sup>14 25–30</sup> In

addition, blood products are sometimes scarce and associated with appreciable expense; decreasing blood transfusion requirements would therefore have health system benefits. Thus, there is compelling rationale to reduce blood loss and blood transfusion as much as possible in patients undergoing liver resection for cancer. A transfusion guidelines document outlining indications for red blood cell (RBC), platelet, frozen plasma and cryoprecipitate transfusion has been created and circulated to all participating sites. The criteria are shown in [table 1](#).

### Antifibrinolytics

In a recent meta-analysis of 95 surgical randomised controlled trials (RCTs) (n=7838 patients), tranexamic acid (TXA) reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval (CI) 0.58 to 0.65; p<0.001).<sup>31</sup> However, the majority of these trials were conducted in cardiac (n=42) and orthopaedic (n=36) surgery, where the mechanism of bleeding is different from abdominal surgery, such as liver resection. Only one RCT has examined the role of perioperative parenteral TXA in patients undergoing liver resection.<sup>32</sup> Among 212 patients who underwent liver resection, the blood transfusion rate was 16% in the control group and 0% in patients who received preoperative TXA (p<0.001). There was no difference in postoperative complications, including thromboembolic events. However, this trial mainly included patients undergoing minor liver resection, with only 18% of patients having major liver resection (≥2 hepatic segments).<sup>33</sup> Additionally, this single-centre trial performed in Taiwan may not be representative of the patients or operative techniques used in North America. Further, the number of events is

**Table 1** HeLiX transfusion protocol

**Indications for RBC transfusion: in patients who are haemodynamically stable, RBC transfusions will be administered 1 unit at a time with reassessment of the patient's symptoms and/or haemoglobin prior to another transfusion.**

Haemoglobin level (g/L)	Indication
<70	Transfusion likely appropriate.
<80	Patients with history of cardiac disease.
70–100	Ongoing blood loss and/or haemodynamic instability intraoperatively; or symptomatic (eg, chest pain, dyspnoea, presyncope, myocardial ischaemia) postoperatively.

**Indications for platelets: dose=1 platelet pool**

Platelet count (×10 <sup>9</sup> /L)	Indication
<50	Significant bleeding.

**Indications for frozen plasma: 3–4 plasma units (10–15 mL/kg)**

INR	Indication
>1.8	Significant bleeding.

**Indications for cryoprecipitate: dose=10 units of cryoprecipitate**

Fibrinogen (g/L)	Indication
<1	Bleeding.
<1.5	Significant bleeding.

HeLiX, haemorrhage during liver resection tranexamic acid; INR, international normalised ratio; RBC, red blood cell.

small and extreme results from small trials tend not to be replicated. As a result of these limitations, results from this trial have not changed practice in North America and most patients do not receive TXA prior to liver resection.

TXA has been studied in various settings at high risk of blood loss, including multisystem trauma, orthopaedic surgery, spine surgery, cardiopulmonary bypass, obstetrics, liver transplantation and liver resection.<sup>7 34–40</sup>

The main side effects of TXA are nausea or diarrhoea. The incidence and severity of these effects are low and they can effectively be treated during the postoperative period. Seizures have also been reported following administration of TXA in cardiac surgery; however, a much higher dose is used in this setting.<sup>41</sup> Seizures have not been observed at a higher frequency than expected in patients receiving the dose of TXA that will be used in this trial. Because TXA is an antifibrinolytic, there has been theoretical concern regarding potential thromboembolic events. Despite this concern, there was no difference in vascular occlusive events between groups in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial (Relative Risk (RR) 0.69; 95% CI 0.44 to 1.07), the World Maternal Antifibrinolytic Trial (RR 0.80; 95% CI 0.44 to 1.43) or in the orthopaedic surgery meta-analysis.<sup>35 42–45</sup> Indeed, in these studies there was actually a trend towards less vascular occlusive events in patients who received TXA, perhaps due to a reduction in perioperative blood transfusion and its associated risks.

### Current practice in Canada

Despite consensus that liver resection is the optimal treatment for most patients with resectable liver malignancies, substantial controversy remains about the optimal management of patients undergoing resection. We conducted a national survey of blood conservation strategies among liver surgeons in Canada. Of 34 respondents, 1 administers TXA frequently, 1 administers TXA selectively and 6 rarely use TXA, while the majority never administer TXA. In the absence of clear evidence, patients receive TXA on the basis of surgeon and anaesthesiologist preference.<sup>46</sup>

### Primary objective

The primary objective is to assess the impact of TXA compared with placebo on receipt of RBC transfusion within 7 days after surgery.

### Secondary objectives

The secondary objectives are to assess the effect of TXA on the following:

- ▶ Receipt of blood transfusion within 7 days of surgery.
- ▶ Intraoperative blood loss.
- ▶ Total blood loss.
- ▶ Postoperative incidence of symptomatic venous thromboembolic event (VTE) within 90 days of surgery.
- ▶ Postoperative incidence of complications within 90 days of surgery.

- ▶ Recurrence-free survival within 5 years of surgery.
- ▶ Overall survival within 5 years of surgery.
- ▶ Quality of life (QoL) at baseline, within 30 days after surgery and 90 days after surgery.
- ▶ Perioperative mortality within 7 days of surgery.
- ▶ Economic analysis.

## METHODS AND ANALYSIS

### Patient and public involvement

The proposal for this trial was discussed by the Hepato-PancreaticoBiliary Community of Surgical ONcologists: Clinical, Evaluative, and Prospective Trials Team (HPB CONCEPT Team). On consultation with expert clinicians and patient partners, this research question was selected to be further developed by the HeLiX (haemorrhage during liver resection tranexamic acid) trial steering committee. The HeLiX trial includes a one-time intervention and minimal follow-up outside of standard of care, and potential to reduce perioperative blood transfusion was found to be relevant to our patient partners. Trial results will be available to the public on ClinicalTrials.gov.

### Study design

This is a multicentre, prospective, blinded, superiority RCT to evaluate the impact of TXA on perioperative blood transfusion in patients undergoing liver resection. Participants will be administered TXA or placebo intravenously after induction of anaesthesia, followed by infusion over 8 hours. Full inclusion and exclusion criteria for the trial are summarised in [table 2](#). This trial has been approved by the research ethics board or institutional review board at participating centres and Health Canada, with Sunnybrook Research Institute as the regulatory sponsor. A list of study sites can be found on ClinicalTrials.gov.

We propose broad eligibility criteria to increase the generalisability and feasibility of the proposed RCT as listed in [table 2](#). The exclusion criteria are predominantly contraindications to antifibrinolytic therapy. There are no exclusions based on gender, race or ethnicity in this trial. This study will be presented to patients through a number of academic and community hospitals across Canada and the USA and will therefore be representative of the gender, racial and ethnic groups in the country who undergo liver resection.

### Recruitment

Research staff will prescreen upcoming clinic lists for patients who may meet the trial eligibility criteria and liaise with a member of the circle of care to approach the patient to discuss the trial informed consent. Patients meeting the eligibility criteria will be recruited preoperatively and written informed consent will be obtained (please see online supplemental file for the sponsor site informed consent form). At the time of enrolment, patients will complete baseline questionnaires including a review of medical history and QoL. Laboratory values (haemoglobin, platelet count, haematocrit, total bilirubin, international normalised ratio and creatinine) will

**Table 2** HeLiX study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>▶ Patient scheduled for open or laparoscopic liver surgery.</li> <li>▶ Age <math>\geq 18</math> years.</li> <li>▶ Cancer-related diagnosis or indication (eg, precancer, suspicion of cancer, definite cancer).</li> </ul>	<ul style="list-style-type: none"> <li>▶ Severe anaemia (haemoglobin level <math>&lt; 90</math> g/L).</li> <li>▶ Documented arterial or venous thromboembolic event at screening or in the past 3 months (not including therapeutic portal vein embolisation).</li> <li>▶ Anticoagulants (other than low-molecular-weight heparin or heparin in prophylactic doses to prevent deep vein thrombosis), direct thrombin inhibitors or thrombolytic therapy administered or completed within last week.</li> <li>▶ Known disseminated intravascular coagulation.</li> <li>▶ Severe renal insufficiency (creatinine clearance <math>&lt; 30</math> mL/min).</li> <li>▶ History of seizure disorder.</li> <li>▶ Pregnant or lactating (a negative urine pregnancy test must be obtained for women of childbearing potential during the pretreatment evaluation).</li> <li>▶ Acquired disturbance of colour vision.</li> <li>▶ Known hypersensitivity to tranexamic acid or any of the ingredients.</li> <li>▶ Unable to receive blood products (ie, difficulty with cross matching, refuses blood transfusion or a history of unexplained severe transfusion reaction).</li> <li>▶ Previously enrolled in this study.</li> </ul>

HeLiX, haemorrhage during liver resection tranexamic acid.

also be obtained. In the event that the patient is unable to come to the hospital or the research team is unable to meet with the patient prior to their scheduled surgery (ie, due to COVID-19 capacity restrictions), the site may obtain verbal consent prior to written consent. Verbal consent must be obtained and documented prior to participant randomisation and before any study procedures occur. If verbal consent is performed, written consent will be obtained prior to the initiation of any study intervention. No biological specimens will be collected as part of this trial. The first participant was enrolled in December 2014 and enrolment is anticipated to be completed by mid-2022 and with primary analysis and publication by the end of 2023. Long-term follow-up data will be available 5 years after enrolment of the last participant.

The trial sample size is based on the primary objective of RBC transfusion. Based on a transfusion incidence of 20%, a total sample size of 1230 patients (615 in each group) will enable us to detect a relative risk reduction in blood transfusion of 30% or greater using a two-sided, two-sample test of proportions at 80% power and alpha of 0.05. We will accrue patients until the sample size of 1230 included patients is achieved, and therefore anticipate recruitment of approximately 1400 patients, to allow for postrandomisation ineligibility (eg, enrolled participant does not receive liver resection or does not receive study drug), dropouts, withdrawals, protocol deviations and incomplete data collection.

### Randomisation

Participants will be randomised to one of two parallel groups: experimental (TXA) or placebo (normal saline). The randomisation code will be generated in random permuted blocks, stratified by centre, using a computer-based randomisation program. The allocation group will be communicated directly to the institutional research pharmacy that will prepare the

blinded intervention for each participant. The code will be retained centrally and only revealed to the investigators once recruitment and data collection are completed. The study schema and outline of this trial are summarised in [figure 1](#). A detailed schedule assessments can be found in [table 3](#).

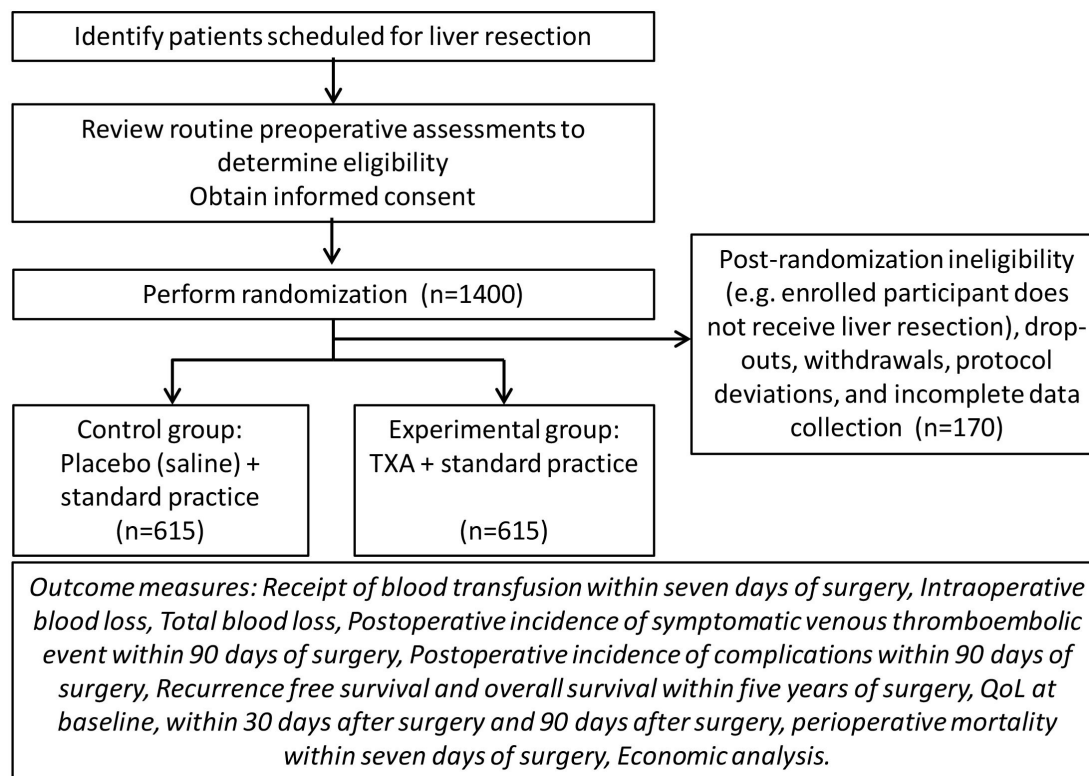
### Interventions

#### Preoperative care (both groups)

All participants will undergo routine preoperative testing to confirm fitness for surgery. No additional tests are required beyond standard of care for patients undergoing liver resection.

#### Intraoperative care (both groups)

All aspects of the liver resection will be left to the surgeon's discretion. Specific techniques used for liver dissection and parenchymal transection in the absence of compelling evidence, including use of portal clamping, ultrasonic or hydrodissection, will not be standardised. Furthermore, surgeons may apply any topical haemostatic agents (other than topical TXA) to the liver surface if it is their usual practice to do so. Use of topical haemostatic agents is documented. All patients will have their CVP maintained as low as possible during anaesthesia, as is routinely performed during liver resection.<sup>13 47 48</sup> Intraoperative crystalloid and colloid fluids will be managed by the anaesthesiologist based on their usual practice. Participants will undergo routine anaesthesia and liver surgery with no additional requirements for this study. Epidural catheters and/or regional blocks for pain management are permitted at the discretion of the anaesthesiologist. All patients will have laboratory investigations performed following the operation and postoperatively per standard of care.



**Figure 1** HeLiX study schema and outline. HeLiX, haemorrhage during liver resection tranexamic acid; QoL, quality of life; TXA, tranexamic acid.

#### Experimental group: TXA

Following induction of anaesthesia and prior to surgical incision (knife-to-skin), the anaesthesiologist will intravenously administer a bolus dose of 1 g TXA in 10 mL of normal saline, administered as a syringe push over 1 min in duration by hand. Following administration of the loading bolus dose of TXA, the anaesthesiologist will begin the intravenous maintenance infusion, 1 g TXA (in 10 mL of normal saline) added to a 250 mL bag of normal saline (approximate total volume determined by site pharmacy based on interpretation of overflow in the 250 mL normal saline bag). The maintenance dose will be administered in a continuous infusion at a rate of 35 mL/hour until the complete dose is given (approximate time of infusion will be 8 hours $\pm$ 30 min). To monitor adherence, the time of bolus administration and the amount given will be recorded. In addition, the start and end time of the infusion and if the entire infusion was administered will be recorded.

The dose of TXA in this trial is based on the CRASH-2 trial, since it is the largest RCT to date that has demonstrated effectiveness of TXA.<sup>34</sup> The optimal dose of TXA was also recently examined in a meta-regression by Ker and colleagues.<sup>31</sup> This systematic review included 104 trials with doses ranging from 5.5 mg/kg to 300 mg/kg. The median dose was 22 mg/kg, with the majority of trials (70%) using a total dose of 30 mg/kg or less. In the meta-regression, the effect of TXA on blood loss did not vary over the dose range assessed (coefficient 0.889, 95% CI 0.787 to 1.004;  $p=0.059$ ). Furthermore, TXA crosses

the blood–brain barrier and may induce seizures at high doses (100 mg/kg or more).<sup>49 50</sup> In an average adult man (70 kg), the CRASH-2 dose is equivalent to 28.5 mg/kg, which is close to the median dose given in these trials and well below the doses given in trials where seizures were observed.

#### Control group: placebo

Following induction of anaesthesia and prior to surgical incision (knife-to-skin), the anaesthesiologist will intravenously administer a bolus dose of 10 mL of normal saline, administered as a syringe push over 1 min in duration by hand. Following administration of the loading bolus dose of normal saline, the anaesthesiologist will begin the intravenous maintenance infusion, 10 mL of normal saline added to a 250 mL bag of normal saline (approximate total volume determined by site pharmacy based on interpretation of overflow in the 250 mL normal saline bag). The maintenance dose will be administered in a continuous infusion at a rate of 35 mL/hour until the complete dose is given (approximate time of infusion will be 8 hours $\pm$ 30 min). To monitor adherence, the time of bolus administration and the amount given will be recorded. In addition, the start and end time of the infusion and if the entire infusion was administered will be recorded.

#### Postoperative care (both groups)

##### Blinding

This is a blinded trial: patients, care providers (surgeons, anaesthesiologists and nurses), data collectors, outcome adjudicators and data analysts will not be aware of group

**Table 3** HeLiX schedule of study assessments

Event	Baseline	POD0	POD1–3	POD4–7	Discharge	POD30±7 days	POD90±14 days	5-year survival	Study exit
Screening	X								
Informed consent	X								
Pretreatment evaluation	X								
Laboratory	X	X	X	X					
Concomitant medications	X	X	X	X	X	X	X		
Quality of life	X					X	X		
Randomisation	X								
Perioperative evaluation		X							
Transfusions		X	X	X	X	X	X		
Postoperative evaluation					X	X	X		
Long-term follow up								X	
Study exit									X

Baseline includes time from screening until surgery and a urine pregnancy test (if applicable).

Pretreatment evaluation includes demographics, diagnosis and medical history.

Laboratory includes haemoglobin, platelet count, haematocrit, creatinine (creatinine clearance), international normalised ratio and bilirubin.

Concomitant medications include anticoagulants, antiplatelets, acetylsalicylic acid, vitamin K and non-steroidal anti-inflammatory drugs.

Quality of life evaluated by EORTC-QLQ-C30 and EORTC-QLQ-LMC21.

Perioperative evaluation includes details of the surgical procedure.

Transfusions include the receipt and number of red blood cell and other blood products transfused.

Postoperative evaluation includes the collection of adverse events until POD7 or discharge (whichever comes first) and complications graded by Clavien-Dindo until POD90.

EORTC, European Organisation for Research and Treatment of Cancer; HeLiX, haemorrhage during liver resection tranexamic acid; LMC21, Liver Metastases Colorectal-21; POD, postoperative day; POD0, day of surgery; QLQ, Quality of Life Questionnaire.

allocation. TXA and placebo medication will be prepackaged into identical individual vials (loading dose syringe and maintenance infusion bag) by the research pharmacy at each participating site. Unblinding may only occur if there is a compelling medical or safety reason to do so and only with approval of the medical monitor.

#### Ancillary and post-trial care

If a patient were to become sick or injured as a direct result of participation in this study, medical care will be provided. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available.

#### Outcome assessment

##### Primary outcome

The primary endpoint is receipt of RBC transfusion over the first 7 postoperative days (POD). The type and number of units of all blood products received will be collected. The primary outcome will be reported as the proportion of participants receiving transfusion.

##### Secondary outcomes

We will collect the following secondary outcomes:

- ▶ Intraoperative blood loss will be assessed by adding the net weight of sponges and fluid suction (minus

irrigation and intraoperative bile or other fluids in suction/sponge).

- ▶ Total blood loss (POD0–POD7) will be assessed by Gross' formula,<sup>51</sup> which uses the maximum postoperative decrease in the level of haemoglobin adjusted for the weight and height of the patient.
- ▶ Number of RBC units transfused (POD0–POD7).
- ▶ Postoperative incidence of symptomatic VTE confirmed with either CT angiogram (for pulmonary embolism) or venous Doppler ultrasound (for deep venous thrombosis) (within 90 days of surgery).
- ▶ Postoperative complications (within 90 days of surgery) will be determined using the Clavien-Dindo classification.<sup>52</sup>
- ▶ Recurrence-free survival (within 5 years of surgery) will be determined by review of patient medical record or via phone call with participant every 6 months until 5 years postsurgery.
  - Recurrence-free survival is defined as the time from POD0 to the first event that is recurrent (local or distal) cancer or death (from any cause).
- ▶ Overall survival (within 5 years of surgery) will be determined by review of patient medical record or via phone call with participant every 6 months until 5 years postsurgery.

- Overall survival is defined as the time from date of POD0 to death from any cause.
- ▶ QoL will be determined by administering the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-C30 and the QLQ-Liver Metastases Colorectal-21 at baseline and at 30 and 90 days following surgery.
- ▶ Perioperative mortality will be recorded between POD0 and POD7.
- ▶ Economic analysis will assess the impact of TXA incorporation on healthcare resources and strategies for systematic utilisation of TXA.

### Criteria for removal from study

The intervention in this trial is an isolated event (TXA during surgery), with postoperative standard of care. The study drug will be discontinued immediately in the event that either of the following occurs: (1) the participant experiences a seizure or (2) the participant does not have a liver resection as planned. With the participant's permission, data will continue to be collected until POD90. For each participant who does not receive a liver resection, an additional participant will be enrolled as replacement. Participants are permitted to withdraw consent at any time if they desire and will not undergo further trial investigations if they do so.

### Data analysis

#### Primary analysis

Receipt of RBC transfusion will be summarised for each group using proportions and the treatment effect will be expressed as the absolute risk difference with 95% CI and compared between groups using  $X^2$  analyses. A beta-binomial model will also be used to determine if there is significant intrasite correlation that needs to be accounted for. Our primary analysis will include only participants randomised to either TXA or placebo who proceeded with liver resection and receive study drug. Participants who were randomised but do not proceed with liver resection or do not receive study drug will not be included.

### Secondary outcomes

#### Secondary analyses

We will conduct a sensitivity analysis whereby all randomised patients are included in the assessment of the primary outcome measure of RBC transfusion. The secondary outcome measures of intraoperative blood loss, total blood loss (POD0–POD7) and number of units transfused (POD0–POD7) will be presented as means with associated SD and compared between groups using two-sample, two-sided t-tests (or Wilcoxon rank-sum tests should there be statistical concerns about the t-test). The secondary outcome measures of incidence of symptomatic VTE and composite complications will be presented as proportions and compared between groups using  $X^2$  analyses. QoL indices will be compared between groups using linear mixed-effect model, adjusting for baseline

QoL and including a time by treatment interaction to estimate the treatment contrast at the primary time-point of interest. Long-term outcomes (within 5 years of surgery) of disease-free survival (suspected), disease-free survival (confirmed) and overall survival will be plotted using Kaplan-Meier curves and analysed with Cox proportional hazards models. For the survival analyses, patients will be subgrouped based on underlying disease that prompted liver resection (eg, colorectal liver metastases, hepatocellular carcinoma, etc).

### Economic analysis

The objective of the economic analysis is to compare the cost of TXA versus placebo on perioperative blood transfusion in patients undergoing liver resection over a 90-day period. We will conduct the analysis using data collected in the RCT from a societal perspective.<sup>53–55</sup> The output of the economic analysis is the incremental cost of TXA compared with placebo (control group). We will analyse the total cost variable as a dependent variable, using regression model, to estimate the difference in expected healthcare cost between the two groups. The intervention variable will be the primary independent variable and the regression model will adjust for potential confounding variables.<sup>56–58</sup>

### Subgroup analyses

We plan to conduct a subgroup analysis comparing the impact of TXA in patients who underwent liver resection of less than four segments compared with those who underwent resection of four or more segments. We plan to fit logistic regression models and include treatment by subgroup interactions to assess whether the magnitude of the treatment effect is significantly different between subgroups. We hypothesise that patients who have larger liver resections (four segments or more) will have greater blood loss and therefore benefit more from TXA.

### Interim analyses

Our approach to interim analyses is guided by a desire to avoid spuriously inflated estimates of treatment effect and the recognition that even if the trial is completed with the current sample size specification and anticipated event incidence there will be a relatively small number of events. Therefore we will not perform interim analyses for efficacy. Our Data Safety Monitoring Board (DSMB) will review any major adverse events/serious adverse events that are potentially attributable to the study drug and all mortalities. Stopping rule guidelines will be detailed in the DSMB charter. In addition the DSMB will perform two interim safety analysis when 30% (n=369) and 50% (n=615) of the study sample have been enrolled.

### Trial and data management

The Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute from St Michael's Hospital and the University of Toronto will be responsible for the trial coordination, site training, site start-up and activation, essential document management, supply management,

database development, data management and statistical analysis. Study data will be entered by each site and maintained on a secure password-protected database developed using REDCap ([www.projectredcap.org](http://www.projectredcap.org)) and will be accessible via the internet. The AHRC will generate data queries sent to site research staff for resolution, in addition to sending newsletter reports to participating sites to maintain frequent communications.

Each site will designate a lead site qualified investigator who may appoint coinvestigators to assist with oversight of protocol-related activities. In addition, each site will also appoint at least one research staff member to perform data entry and other duties. A delegation of responsibilities log will be completed at each site prior to activation to document all delegated trial responsibilities to investigators and research staff. For each individual on the delegation of responsibilities log, appropriate clinical research and trial specific training will be collected.

### Data confidentiality

Participant data collected on paper case report forms will be de-identified and kept in locked filing cabinets in locked offices and transcribed to the secure, password-protected database (REDCap). The study sponsor will have access to the final trial data set. Site principal investigators will have access to their own site's data.

## ETHICS AND DISSEMINATION

### Ethics

Written informed consent to participate will be obtained from all participants at a total of 10 sites in Canada and 1 site in the USA. This trial has been approved by Health Canada (parent control number 177992) and the ethics boards at the following sites: Research Ethics Board of Sunnybrook Health Sciences Centre (3441); Conjoint Health Research Ethics Board (14-1747\_MOD7); McGill University Health Centre Research Ethics Board (2015-2015, 14-298-BMA, eReviews\_4211, 14-298-MUHC-T); Nova Scotia Health Authority Research Ethics Board (1019252); University Health Network Research Ethics Board (14-8208); The Queens University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (6021513); Hamilton Integrated Research Ethics Board (3352); Unity Health Toronto Research Ethics Office (17-824); Western University Health Sciences Research Ethics Board (109393); Interior Health Research Ethics Board (2018-19-013-I); and Mayo Clinic Institutional Review Boards (19-001040).

### Dissemination

Once available, results will be posted to ClinicalTrials.gov. In addition, results will be shared with participating healthcare providers and the general medical community through local and international meetings, presentation and publication.

### Impact

This trial is supported by the HPB CONCEPT Team. The HPB CONCEPT Team was created in 2011 to improve the

care of patients with hepatopancreaticobiliary cancers through investigator-initiated research and to provide a forum for developing high-impact clinical trials. The HPB CONCEPT Team identified the investigation of TXA in patients undergoing liver resection as a priority research area with full endorsement.

Clinical practice worldwide would change if this trial demonstrates that TXA use in liver resection decreases transfusions. Over 2000 patients in Canada, and many more in other countries, undergo liver resection annually and could benefit from this simple, low-cost intervention. The results may stimulate trials in other areas in which transfusion is common and TXA is not currently used.

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## REFERENCES

- 1 Beard SM, Holmes M, Price C, *et al*. Hepatic resection for colorectal liver metastases: a cost-effectiveness analysis. *Ann Surg* 2000;232:763–76.
- 2 Lin TY, Lee CS, Chen KM, *et al*. Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience. *Br J Surg* 1987;74:839–42.
- 3 Man K, Fan ST, Ng IO, *et al*. Prospective evaluation of Pringle maneuver in hepatectomy for liver tumors by a randomized study. *Ann Surg* 1997;226:704–13.
- 4 Poon RT, Fan ST, Lo CM, *et al*. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 2004;240:698–710.
- 5 Ramos E, Dalmau A, Sabate A, *et al*. Intraoperative red blood cell transfusion in liver transplantation: influence on patient outcome, prediction of requirements, and measures to reduce them. *Liver Transpl* 2003;9:1320–7.
- 6 McColl RJ, Brar B, Ghali WA, *et al*. Hepatic resection in Canada: rates and geographic variation. *Can J Surg* 2009;52:E264–8.
- 7 Alkozai EM, Lisman T, Porte RJ. Bleeding in liver surgery: prevention and treatment. *Clin Liver Dis* 2009;13:145–54.
- 8 Friedman LS. The risk of surgery in patients with liver disease. *Hepatology* 1999;29:1617–23.
- 9 Groenland THN, Porte RJ. Antifibrinolytics in liver transplantation. *Int Anesthesiol Clin* 2006;44:83–97.
- 10 Gurusamy K, Sheth H, Kumar Y. Methods of vascular occlusion for elective liver resections. *Cochrane Database Syst Rev* 2009;21:CD007632.
- 11 Lesurtel M, Selzner M, Petrowsky H. A prospective randomized study in 100 consecutive patients: comparing four different transection strategies how should transection of the liver be performed. *Ann Surg* 2005;242:814–23.
- 12 Poon RTP. Current techniques of liver transection. *HPB* 2007;9:166–73.
- 13 McNally SJ, Revie EJ, Massie LJ, *et al*. Factors in perioperative care that determine blood loss in liver surgery. *HPB* 2012;14:236–41.
- 14 Kooby DA, Stockman J, Ben-Porat L, *et al*. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003;237:860–70.
- 15 Jarnagin WR, Gonen M, Maithel SK, *et al*. A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. *Ann Surg* 2008;248:360–9.
- 16 Bui LL, Smith AJ, Bercovici M, *et al*. Minimising blood loss and transfusion requirements in hepatic resection. *HPB* 2002;4:5–10.
- 17 Gozzetti G, Mazziotti A, Grazi GL, *et al*. Liver resection without blood transfusion. *Br J Surg* 1995;82:1105–10.
- 18 Jamieson GG, Corbel L, Campion JP, *et al*. Major liver resection without a blood transfusion: is it a realistic objective? *Surgery* 1992;112:32–6.
- 19 Katz SC, Shia J, Liau KH, *et al*. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg* 2009;249:617–23.
- 20 Kusano T, Sasaki A, Kai S, *et al*. Predictors and prognostic significance of operative complications in patients with hepatocellular carcinoma who underwent hepatic resection. *Eur J Surg Oncol* 2009;35:1179–85.
- 21 Rees M, Plant G, Wells J, *et al*. One hundred and fifty hepatic resections: evolution of technique towards bloodless surgery. *Br J Surg* 1996;83:1526–9.
- 22 Ryan JA, Faulkner DJ. Liver resection without blood transfusion. *Am J Surg* 1989;157:472–5.
- 23 Mayo SC, Shore AD, Nathan H, *et al*. Refining the definition of perioperative mortality following hepatectomy using death within 90 days as the standard criterion. *HPB* 2011;13:473–82.
- 24 Delaney M, Wendel S, Bercovitz RS, *et al*. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* 2016;388:2825–36.
- 25 Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg* 2012;256:235–44.



- 26 Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006;1:CD005033.
- 27 Heiss MM, Mempel W, Delanoff C, et al. Blood transfusion-modulated tumor recurrence: first results of a randomized study of autologous versus allogeneic blood transfusion in colorectal cancer surgery. *J Clin Oncol* 1994;12:1859–67.
- 28 Kneuertz PJ, Patel SH, Chu CK, et al. Effects of perioperative red blood cell transfusion on disease recurrence and survival after pancreaticoduodenectomy for ductal adenocarcinoma. *Ann Surg Oncol* 2011;18:1327–34.
- 29 Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. *Transfusion* 1995;35:760–8.
- 30 Zakaria S, Donohue JH, Que FG, et al. Hepatic resection for colorectal metastases: value for risk scoring systems? *Ann Surg* 2007;246:183–91.
- 31 Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ* 2012;344:e3054.
- 32 Wu C-C, Ho W-M, Cheng S-B, et al. Perioperative parenteral tranexamic acid in liver tumor resection: a prospective randomized trial toward a "blood transfusion"-free hepatectomy. *Ann Surg* 2006;243:173–80.
- 33 Pang YY. The Brisbane 2000 terminology of liver anatomy and resections. *HPB* 2000; 2:333–39. *HPB* 2002;4:333–9.
- 34 CRASH-2 trial Collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23–32.
- 35 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:2106–16.
- 36 Sentilhes L, Winer N, Azria E, et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. *N Engl J Med* 2018;379:731–42.
- 37 Kagoma YK, Crowther MA, Douketis J, et al. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. *Thromb Res* 2009;123:687–96.
- 38 Karkouti K, Rampersaud Y, McCluskey S. Blood conservation in elective spine surgery. *Can J Anaesth* 2002;49:A12.
- 39 Wang G, Xie G, Jiang T, et al. Tranexamic acid reduces blood loss after off-pump coronary surgery: a prospective, randomized, double-blind, placebo-controlled study. *Anesth Analg* 2012;115:239–43.
- 40 Wong J, El Beheiry H, Rampersaud YR, et al. Tranexamic acid reduces perioperative blood loss in adult patients having spinal fusion surgery. *Anesth Analg* 2008;107:1479–86.
- 41 Lecker I, Wang D-S, Whissell PD, et al. Tranexamic acid-associated seizures: causes and treatment. *Ann Neurol* 2016;79:18–26.
- 42 Fergusson DA, Hébert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008;358:2319–31.
- 43 Henry DA, Carless PA, Moxey AJ. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011;16:CD001886.
- 44 Makwana J, Paranjape S, Goswami J. Antifibrinolytics in liver surgery. *Indian J Anaesth* 2010;54:489–95.
- 45 Roberts I, Shakur H, Ker K. CRASH-2 trial Collaborators. antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev* 2011;1:CD004896.
- 46 Truong JL, Cyr DP, Lam-McCulloch J, et al. Consensus and controversy in hepatic surgery: a survey of Canadian surgeons. *J Surg Oncol* 2014;110:947–51.
- 47 Giordano C, Deitte LA, Gravenstein N, et al. What is the preferred central venous pressure zero reference for hepatic resection? *Anesth Analg* 2010;111:660–4.
- 48 Rahbari NN, Koch M, Zimmermann JB, et al. Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection: a randomized controlled trial. *Ann Surg* 2011;253:1102–10.
- 49 Kalavrouziotis D, Voisine P, Mohammadi S, et al. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *Ann Thorac Surg* 2012;93:148–54.
- 50 Murkin JM, Falter F, Granton J, et al. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010;110:350–3.
- 51 Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology* 1983;58:277–80.
- 52 Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;250:187–96.
- 53 Canadian Institute for Health Information. Patient cost estimator, 2019. Available: <https://www.cihi.ca/en/patient-cost-estimator> [Accessed 07 Oct 2019].
- 54 Canadian Institute for Health Information. Cost of a standard hospital stay, 2017. Available: <https://yourhealthsystem.cihi.ca/hsp/inbrief%3Bjsessionid=T10N-pfyq6TvKmMp4qn+pXlw.yhs?lang=en#!/indicators/015/cost-of-a-standard-hospital-stay;/mapC1;mapLevel2;/> [Accessed 07 Oct 2019].
- 55 Canadian Institute for Health Information. The cost of acute care hospital stays by medical condition in Canada, 2004–2005, 2008. Available: [https://secure.cihi.ca/free\\_products/nhex\\_acutecare07\\_e.pdf](https://secure.cihi.ca/free_products/nhex_acutecare07_e.pdf) [Accessed 07 Oct 2019].
- 56 Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.
- 57 Briggs A, Nixon R, Dixon S, et al. Parametric modelling of cost data: some simulation evidence. *Health Econ* 2005;14:421–8.
- 58 Glick HA, Doshi JA, Sonnad SS. *Economic evaluation in clinical trials*. 2nd edn. Oxford University Press, 2014.