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Hospital policy of tranexamic acid to reduce transfusion in major non-cardiac surgery (TRACTION): protocol for a phase IV randomised controlled trial

Brett L Houston ,[1] Daniel I McIsaac ,[2,3] Rodney H Breau,[2,3] Meghan Andrews,[2] Sinziana Avramescu,[4] Hema Bagry,[5] Robert F Balshaw ,[5] Jayesh Daya,[5] Kaitlin Duncan,[6] Christopher Harle,[7] Eric Jacobsohn,[5] Tina Kerelska,[4] Sarah McIsaac,[6] Tim Ramsay ,[3] Tarit Saha,[8] Iris Perelman,[3] Angela Recio,[5] Dayna Solvason,[5] Daniel Szoke,[7] Marshall Tenenbein,[5] Dean A Fergusson ,[3] Ryan Zarychanski[1]

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BLH and DIM contributed equally.
DAF and RZ contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Daniel I McIsaac; dmcisaac@toh.ca

ABSTRACT

Introduction Tranexamic acid (TXA) is an inexpensive and widely available medication that reduces blood loss and red blood cell (RBC) transfusion in cardiac and orthopaedic surgeries. While the use of TXA in these surgeries is routine, its efficacy and safety in other surgeries, including oncologic surgeries, with comparable rates of transfusion are uncertain. Our primary objective is to evaluate whether a hospital-level policy implementation of routine TXA use in patients undergoing major non-cardiac surgery reduces RBC transfusion without increasing thrombotic risk.

Methods and analysis A pragmatic, registry-based, blinded, cluster-crossover randomised controlled trial at 10 Canadian sites, enrolling patients undergoing non-cardiac surgeries at high risk for RBC transfusion. Sites are randomised in 4-week intervals to a hospital policy of intraoperative TXA or matching placebo. TXA is administered as 1 g at skin incision, followed by an additional 1 g prior to skin closure. Coprimary outcomes are (1) effectiveness, evaluated as the proportion of patients transfused RBCs during hospital admission and (2) safety, evaluated as the proportion of patients diagnosed with venous thromboembolism within 90 days. Secondary outcomes include: (1) transfusion: number of RBC units transfused (both at a hospital and patient level); (2) safety: in-hospital diagnoses of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism; (3) clinical: hospital length of stay, intensive care unit admission, hospital survival, 90-day survival and the number of days alive and out of hospital to day 30; and (4) compliance: the proportion of enrolled patients who receive a minimum of one dose of the study intervention.

Ethics and dissemination Institutional research ethics board approval has been obtained at all sites. At the completion of the trial, a plain language summary of the results will be posted on the trial website and distributed in the lay press. Our trial results will be published in a peer-reviewed scientific journal.

Trial registration number NCT04803747.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The cluster crossover design builds on existing knowledge of tranexamic acid (TXA) use in non-cardiac surgery by evaluating the implementation of a hospital-level policy.
⇒ Tranexamic acid to reduce transfusion in major non-cardiac surgery (TRACTION) is powered to evaluate the effectiveness of TXA in the context of safety, thereby directly informing a clinician's risk–benefit assessment and therapeutic decision-making.
⇒ The use of routinely collected clinical data increases efficiency and substantially reduces trial costs.
⇒ TRACTION site participation is limited by those with registry data capabilities; however, trial results are expected to be widely generalisable.
⇒ TRACTION will enrol a broad, heterogenous at-risk patient population with diverse mechanisms of bleeding, but is sufficiently powered to detect clinically relevant transfusion outcomes within specific surgical subtypes.

INTRODUCTION

Perioperative bleeding is a major indication for red blood cell (RBC) transfusion and the third most common reason for transfusion among hospitalised patients.[1 2] RBC transfusions are a scarce and costly resource associated with adverse patient outcomes.[3] Interventions to reduce perioperative transfusion are endorsed by health authorities and professional societies.[4 5]

Tranexamic acid (TXA) is an inexpensive and widely available antifibrinolytic drug given broadly to patients with increased local fibrinolysis and hyperfibrinolysis such as during haemorrhage, trauma and surgery. In cardiac surgery and hip and knee arthroplasty, TXA reduces RBC transfusion and

its administration is considered standard of care.[6] In the POISE-3 (Tranexamic Acid in Patients Undergoing Noncardiac Surgery) trial that evaluated TXA in adults undergoing non-cardiac surgery who were at risk for bleeding or cardiovascular complications, TXA reduced the composite of life-threatening bleeding, major bleeding and bleeding into a critical site compared with placebo.[7] Non-inferiority was not established for the primary composite safety outcome of cardiovascular thrombotic adverse events, although event rates were low and the absolute difference between groups was small.

Building on the results of POISE-3, we aim to evaluate whether the implementation of a hospital-level policy of TXA administration can safely reduce RBC transfusion in a broad patient population undergoing major non-cardiac surgery. If safe and effective, results would forward a new standard of care, reduce costs and promote the sustainability of blood supplies.

METHODS AND ANALYSIS

Trial objectives

To establish whether a hospital-level implementation strategy of routine TXA use in patients undergoing major non-cardiac surgery reduces RBC transfusion without increasing thrombotic risk.

Trial design

We are performing a pragmatic, multicentre, blinded registry-based cluster crossover randomised controlled trial to evaluate whether a hospital policy of perioperative TXA use among patients undergoing major non-cardiac surgery safely reduces perioperative RBC transfusion compared with placebo. Hospital-based time periods are the unit of randomisation (clusters). All hospitals are allocated to TXA or placebo treatment in 4-week intervals. Trial enrolment started in March 2021, and the end of trial follow-up and analysis is anticipated in January 2025.

Trial population

The trial is being conducted at 10 hospitals (clusters) in Canada with substantive non-cardiac surgery programmes.

Inclusion criteria

Cluster-level inclusion criteria: hospital sites will be included if the site performs ≥100 non-cardiac surgeries per month and if both anaesthesia and hospital leadership agree to manage patients as per the policy being implemented and evaluated in the trial.

Patient-level inclusion criteria: patients ≥18 years of age undergoing major non-cardiac 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.[8 9] Patient eligibility criteria is broad to allow evaluation of treatment effect across a comprehensive range of patients seen at the hospital to ensure generalisability of findings. Examples of eligible surgeries are included in online supplemental appendix 1.

Exclusion criteria

Exclusion criteria include active thromboembolic disease (ie, arterial or venous thrombosis within 90 days preoperative) due to theoretical concern regarding the use of an antifibrinolytic medication risk in this setting; cardiac and hip or knee total hip arthroplasty because TXA is routinely used in these settings; surgeries with free flap reconstruction due to concern for microvascular thrombosis; trauma surgery where TXA was administered within the prior 3 hours and pregnancy because limited data exist in this setting.

Trial interventions

Intervention group

The intervention arm will receive TXA 1 g bolus (2 g for patients over 100 kg) intravenously administered within 10 min of the first surgical incision, followed by an additional 1 g given intravenously prior to skin closure, at the discretion of the anaesthesiologist (eg, intravenous bolus at 2–4 hours of surgery, at skin closure or the additional 1 g given as a continuous infusion throughout the surgical procedure).

The TXA dose and dosing schedule in tranexamic acid to reduce transfusion in major non-cardiac surgery (TRACTION) is pragmatic, easy to implement and follow at a hospital level, supported by the existing literature, and emulates the variable dosing strategies used in current practice.[10 11] As examples of variable dosing used in clinical trials and in practice: in a recently published trial of TXA in non-cardiac surgery, patients received a 1 g bolus at the start and end of surgery.[7] In a trial of TXA in major trauma, a 1 g TXA bolus followed by a 1 g infusion over 8 hours reduced RBC transfusion and improved survival.[12] In a large trial of TXA to treat post-partum haemorrhage, a 1 g TXA bolus, with an option to administer an additional bolus if bleeding continued, reduced bleeding and death due to bleeding.[13] In TRACTION, the 1 g bolus administered will be sufficient to achieve therapeutic plasma TXA concentrations.[14–16] Given the mean surgery duration in our eligible population is 3.5 hours (SD 2.1) hours,[17] our proposed dosing strategy is expected to maintain therapeutic plasma TXA concentration for the duration of the surgery.[18] In formal stakeholder engagement interviews, the TRACTION dosing schedule is feasible in the setting of a pragmatic trial and will facilitate global adoption if found to be effective and safe.

Control group

The control arm will receive matching placebo bolus(es) ± infusion (0.9% sodium chloride).

Although designed as a pragmatic trial, a placebo arm is required to preserve the validity of the trial outcomes. Given the hypothesised reduction in bleeding and transfusion, the use of an open-label design with usual care as the comparator could increase the risk of contamination

(ie, use of TXA) due to changes in practice over time supporting greater TXA use. For our superiority outcome of transfusion, contamination would appear to decrease the effectiveness of a hospital-level policy to universally adopt TXA. With regard to our non-inferiority safety outcome of venous thromboembolism, contamination could bias the trial towards non-inferiority and increase the probability of missing important safety signals should they exist.

Cointerventions

Perioperative cointerventions, including but not limited to, cell salvage, topical TXA use and intraoperative thromboprophylaxis will be documented, but not protocolised. The decision to transfuse blood products is at the discretion of the treating physicians. Any drugs or procedures thought to be required as 'rescue' therapies are permitted at the discretion of the surgical team.

Trial outcomes

Primary outcomes

Designed to inform routine clinical decision-making, we have selected coprimary outcomes that evaluates effectiveness in the context of safety. Our coprimary outcomes are (1) the proportion of patients transfused RBCs during the index hospitalisation (effectiveness) and (2) the incidence of deep vein thrombosis or pulmonary embolism (collectively called venous thromboembolic (VTE) disease) within 90 days of surgery (safety).

Our primary outcomes inform a patient's, surgeon's and anaesthesiologist's and a hospital policy decision to use TXA whereby the expected benefits are placed in the context of potential harm. Safely reducing perioperative RBC transfusions will mitigate reliance on the blood supply. These outcomes reflect the specific views and input of clinician knowledge users, our patient committee and key stakeholders.

Secondary outcomes

The following outcomes will be assessed:

1. Transfusion: the number of RBC units transfused (both at a hospital and patient level). This will be evaluated at 3 and 7 days postoperative and at hospital discharge.
2. Safety: *in-hospital* diagnoses of myocardial infarction (MI), stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE).
3. Clinical: hospital length of stay, intensive care unit (ICU) admission, hospital survival, 90-day survival and the number of days alive and out of hospital to day 30 (a patient-centred outcome that integrates length of stay, readmission and early deaths after surgery into a single outcome metric[19]).
4. Compliance: the proportion of enrolled patients who receive a minimum of one dose of the study intervention.

Recruitment and patient consent

Patients undergoing major non-cardiac surgery who meet trial inclusion criteria are electronically identified preoperatively using a surgical summary report generated from an electronic surgical booking system. Research coordinators regularly review the surgical slate to identify patients undergoing non-cardiac surgery at high-risk (≥5%) of RBC transfusion.

TXA is a widely available, low-risk medication with an established safety profile and is broadly approved for use in conditions associated with local fibrinolysis.[6 7 9] The study intervention also falls within the variable practice that defines usual care (ie, those undergoing a high-risk surgery currently may or may not receive TXA at the discretion of the anaesthesiologist and/or surgeon). As such, patients are enrolled using either altered or waived consent, as per local research ethics board instruction and approval. Details pertaining to the altered consent model are included in online supplemental appendix 2. Individual patients retain the right to withdraw from the study at any time.

Methods of data collection and duration of follow-up

To enable TRACTION, we demonstrated our ability to identify and link required trial data from robust and validated primary data sources to facilitate reliable outcome ascertainment. Using the Surgical Management Information System and Discharge Abstract Database at each hospital, regional or national transfusion databases and provincial administrative data, we are electronically capturing patient demographics and comorbidities, surgery specifics, our primary transfusion and safety outcomes, as well as secondary clinical outcomes.

A short case report form is used to capture the administration of the study drug and to confirm essential data elements not uniformly available at all sites through existing electronic registries (online supplemental appendix 3). We are obtaining 90-day VTE outcomes from provincial administrative sources using a validated combination of physician billing and imaging codes[20 21] (online supplemental appendix 4).

Risk and methods to protect against bias

Randomisation and allocation concealment

Over the duration of the trial, participating sites are centrally and randomly allocated to receive either TXA or matching placebo at 4-week intervals. The treatment group allocation will be assigned using a central, secure, web-based randomisation system. A statistician not otherwise involved in the trial is generating the randomised allocation sequence, and the intervention assignment is restricted to research pharmacy staff preparing the investigational product specific to the interval assignment. To minimise sources of selection and ascertainment bias, anaesthesiologists, surgeons, investigators and research staff are blinded to randomisation schemes and treatments administered.

Confirmation of TXA dosing

In the event of life-threatening haemorrhage, should the surgical team require confirmation of TXA administration

(rather than placebo), then blinded emergency investigational product will be available to preserve blinded site allocation assignment. The emergency investigational product will contain the opposite of the site's randomisation (either TXA or placebo). To ensure sufficient distinction and prevent erroneous administration, the investigational product uses white labels whereas the emergency investigational product has fluorescent labels. Further, the batch numbers of both investigational product and emergency investigation product are documented on the case report form. Given the cluster trial design, this procedure abrogates the need for emergency unblinding, which could compromise the site pair for the randomisation period.

Emergency unblinding

Given the established safety profile of TXA, and our confirmation of TXA dosing procedure, the need for emergency unblinding is unlikely to be required. However, if emergent knowledge of treatment assignment is felt to be necessary to provide patient care, the anaesthesiologist or surgeon will contact the unblinded site research pharmacist.

Analytic plan

Sample size and power calculations

The TRACTION trial has been designed with two coprimary outcomes. The total sample size of approximately 8320 patients reflects the power needed to inform the safety outcome of VTE. The statistical analytic plan is included as online supplemental appendix 5.

Transfusion (effectiveness; superiority): informed by our large observational study,[8 10] the average cluster-period size is predicted to be approximately 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 eight clusters randomly assigned to minimum of eight 4-week periods, the trial 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%.[22]

Venous thromboembolism (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 4-week periods, TRACTION will have 83% power to exclude a 1% or greater increase in VTE at 90 days from a predicted baseline rate of 2.2%.[9] As study analyses require direct calculation of intervention effects on a relative (ie, OR) 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 OR excludes 1.47, we will conclude non-inferiority).

Placing effectiveness in the context of safety, TRACTION is likely overpowered to evaluate the superiority of our coprimary transfusion effectiveness outcome within the enrolled population, but adequately powered to detect a clinically relevant increase in thrombosis. Since each of the two coprimary hypotheses must be satisfied to deem TXA beneficial, the type I error rate is preserved without the need for multiplicity adjustments.[23]

Analysis of coprimary outcomes

We will analyse our primary superiority outcome (proportion of transfused) using an intent-to-treat analysis (ITT). Since ITT can bias to the null and lead to false claims of non-inferiority, we will analyse our primary non-inferiority outcome (VTE within 90 days) using both per-protocol (primary analysis for this outcome) and ITT populations. A favourable trial conclusion will require the primary analyses of both outcomes to yield acceptable results. The ITT population will include all randomised patients. We expect that virtually all outcomes will be available from routinely collected data. The per-protocol population will include all patients, with the exception of those allocated to the TXA arm who did not receive intravenous TXA and those allocated to the placebo arm who received intravenous TXA. All primary outcome analyses will be at an individual patient level.

Between-group event rates for the primary superiority outcome (proportion transfused RBC units during the index hospitalisation) will be estimated using a mixed effects logistic regression model, as outlined in the statistical analytic plan (online supplemental appendix 5). Our primary non-inferiority analysis will test the difference in VTE events within 90 days postoperatively between groups by examining the one-sided 97.5% CI for the OR using the same regression model. The absolute risk difference and its CI will be computed as the proportion in the TXA group minus the proportion in the placebo group. If the upper limit of the 97.5% CI excludes the non-inferiority margin of 1%, non-inferiority will have been established (equivalent to if the upper bound of the one-sided 97.5% CI of the OR excludes 1.47). Our primary analyses will be unadjusted. In sensitivity analyses, we will compare between-group differences in event rates for the primary superiority (RBC transfusion) and safety (VTE) outcome adjusted for age, sex, surgery type, surgical urgency and preoperative haemoglobin concentration using hierarchical logistic regression analysis. See online supplemental appendix 5 for complete details of the statistical analytic plan.

Analysis of secondary outcomes

The absolute differences in the dichotomous secondary outcomes (in-hospital diagnosis of MI, 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. The results will be expressed as HRs with 95% CIs. Consistent with our primary outcomes, analysis of all secondary outcomes will be unadjusted. In sensitivity analyses, these outcomes will be estimated adjusting for age, sex, surgery type, surgical urgency and preoperative haemoglobin concentration.

Subgroup and sensitivity analyses

The treatment effect modification for both coprimary outcomes will be investigated through the inclusion of interaction terms in the main adjusted model. Candidate effect modifiers include age, surgery type, surgical urgency, transfusion risk and cancer status.

Interim analyses

Given the short anticipated duration of enrolment (approximately 8–12 months), low rates of VTE reported in published trials, and the requirement for 90 day follow-up for VTE incidence, 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. The trial data safety monitoring board (DSMB) will convene mid-way through the trial (estimated 4–5 months after trial initiation) to review trial processes, enrolment and adverse events.

Risks to the safety of potential participants

TXA is not known to be associated with an increased risk of adverse events when used in non-cardiac surgery. In cardiac surgery, rare events of seizure activity have been described during 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. Specifically, serious adverse events constitute seizure activity or allergic reactions that result in death, are life-threatening, prolong hospitalisation, cause significant disability or incapacity, or cause another condition judged as serious.

Data monitoring

The trial data and compliance will be monitored using electronic remote data validation. This promotes data accuracy, completeness, consistency with source documents and prioritises participant protection.

Study management and governance

The overall management of the TRACTION trial is coordinated at the University of Manitoba (Winnipeg, Manitoba, Canada). The Ottawa Methods Centre located at the Ottawa Hospital Research Institute (Ottawa, Ontario, Canada) is responsible for generating the randomisation scheme, hosting web-based enrolment, data management, data validation and statistical analyses. Individual site principal investigators are responsible for ensuring trial conduct at their respective sites. A steering committee is responsible for providing clinical and methodological guidance pertaining to the trial design, execution, analysis and publication of the main trial results.

Patient and public involvement

The design and conduct of TRACTION was informed by active involvement of our patient partners. In March 2018, we established a patient advisory committee comprised of patients or family members of patients who required major non-cardiac surgery and required a blood transfusion. Through our patient advisory committee, in the context of committee meetings, surveys and electronic communications, we finalised the type of trial (patient randomised vs cluster), planned the timing and methods of consent and informational study materials. Patients and caregivers provided critical input into trial design, processes and outcomes. With safety in mind, the patient voice was essential when selecting safety as our coprimary outcome that prioritises safety. Secondary outcomes were also finalised through shared dialogue, and it was our patient committee that specifically forwarded days alive and out of hospital as a secondary outcome. Given the cluster design of the trial, individual patients will not receive study results, although we will work with our patient partners to meaningfully disseminate trial results to the public.

ETHICS AND DISSEMINATION

Institutional research ethics board approval has been obtained at all sites (online supplemental appendix 6). All protocol modifications will be approved by the sponsor and individual site REBs prior to implementation. All trial data and datasets will be deidentified and linked using a unique participant identifier. The final trial dataset will be retained within the Institute for Clinical Evaluative Sciences.

All aspects of the TRACTION research programme have integrated core components of the knowledge-to-action cycle to facilitate incorporation into current evidence and ensure widespread uptake of new knowledge generated.[24] We have identified an important clinical problem and justified our trial with observational research and knowledge syntheses manuscripts. Stakeholders have been surveyed to assess the relevancy of the research question, identify barriers to knowledge use and investigate clinical equipoise. The trial design, including the incorporation of coprimary outcomes and altered methods of consent, has been developed with knowledge users, decision-makers and patients. Following completion of the trial, a plain language summary of the trial results will be posted to the trial website (tractiontrials.org) and distributed in the lay press. Leadership at participating clusters (hospitals) will be forwarded a summary/interpretation of the trial. At the completion of the trial, we will work with our patient-partners, decision-makers and policymakers to create a knowledge translation strategy so the results of the trial widely impacts perioperative surgical policy.

DISCUSSION

TRACTION is expected to demonstrate that implementation of a hospital-level policy strategy of TXA safely reduces RBC transfusion in patients undergoing major non-cardiac surgeries at high risk for transfusion. The cluster crossover design of TRACTION builds on existing knowledge of TXA use in non-cardiac surgery by evaluating the implementation of a hospital-level policy strategy. Cluster trials are appropriate trial designs to inform important policy decision. The cluster crossover design was used to maximise precision and minimise loss of statistical power that arises in cluster trials due to the intracluster correlation (where patients within a cluster are more similar than patients across clusters). In this type of trial, clusters will randomly, and without a site's knowledge, crossover from the intervention to placebo groups multiple times over the duration of the trial. This study design is consistent with how other effective perioperative practices such as preoperative surgical safety checklists, perioperative use of antibiotics and surgical sponge counts have been studied, standardised and introduced as hospital-level policies.[25–27] When administered to highly selected groups of patients undergoing major non-cardiac surgery, and in the context of explanatory (vs pragmatic) trials, TXA consistently reduces transfusion without evidence of increased thrombotic risk.[7 9] Given the large numbers of patients undergoing major non-cardiac surgery, generalisable evidence that TXA is safe and effective is required. The generation of such evidence will necessitate the inclusion of patient populations not well represented in previous trials, as well as a design that reflects a policy-level change in practice.

While the registry-based design of TRACTION limited site participation to those with registry data capabilities, trial results are expected to be widely generalisable. TRACTION will enrol a broad, heterogenous at-risk patient population with diverse mechanisms of bleeding, but is sufficiently powered to detect clinically relevant transfusion outcomes within specific surgical subtypes.

TRACTION is powered to evaluate the effectiveness of TXA in the context of safety, thereby directly informing a clinician's risk–benefit assessment and therapeutic decision-making. Trial results will inform a new standard of care for patients undergoing high-risk major non-cardiac surgery and promote the sustainability of blood supplies. The use of routinely collected clinical data increases efficiency and substantially reduces trial costs, thereby demonstrating that large, practice-changing and cost-efficient trials can be conducted using existing routinely collected data.

Author affiliations
[1]Hematology and Medical Oncology, University of Manitoba/CancerCare Manitoba, Winnipeg, Manitoba, Canada
[2]University of Ottawa, Ottawa, Ontario, Canada
[3]Ottawa Hospital Research Institute (OHRI), Ottawa, Ontario, Canada
[4]Humber River Regional Hospital, Toronto, Ontario, Canada
[5]University of Manitoba, Winnipeg, Manitoba, Canada
[6]Northern Ontario School of Medicine, Sudbury, Ontario, Canada
[7]Western University, London, Ontario, Canada
[8]Queen's University, Kingston, Ontario, Canada

Contributors All authors were involved in the process of study protocol design and manuscript review. BLH, DIM, RHB, DAF and RZ initially drafted the manuscript. RFB and TR drafted the analytic plan. BLH, DIM, RHB, MA, SA, HB, RFB, JD, KD, CH, EJ, TK, SM, TR, TS, IP, AR, DSo, DSz, MT, DAF and RZ reviewed and edited the manuscript and provided final manuscript approval.

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ORCID iDs
Brett L Houston http://orcid.org/0000-0002-8776-4083
Daniel I McIsaac http://orcid.org/0000-0002-8543-1859
Robert F Balshaw http://orcid.org/0000-0002-2455-8792
Tim Ramsay http://orcid.org/0000-0001-8478-8170
Dean A Fergusson http://orcid.org/0000-0002-3389-2485

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