HEMOglobin transfusion threshold in Traumatic brain Injury Optimization: The HEMOTION TRIAL PROTOCOL

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Canadian Critical Care Trials Group
Canadian Traumatic Brain Injury Research Consortium

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Site Principal Investigator’s Statement and Signature:

I have reviewed this protocol and comprehend the study design. I accept to participate as a Site Principal Investigator and to abide to the protocol as outlined. I understand that I shall not disclose any unpublished information included in the protocol without receiving the authorization from the Steering Committee of the trial. The trial shall be conducted according to GCP and all applicable regulatory requirements.

_________________________________________ ________________
Signature: Site Principal Investigator Date
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1. Abstract

**Background:** Most trauma deaths are related to traumatic brain injury (TBI). Although the management of patients has improved, mortality remains unacceptably high, and half of survivors of moderate and severe TBI are left with major functional impairment. Current management guidelines are based on limited evidence and practice is highly variable. Most acutely ill patients with TBI will develop anemia, which may decrease oxygen delivery to a fragile brain. While clinical practice is moving towards transfusing at low hemoglobin (Hb) levels, experts have expressed concerns regarding restrictive strategies, which may adversely affect clinical outcomes in TBI.

**Objectives:** Our primary objective is to evaluate the effect of red blood cell (RBC) transfusion thresholds on neurological functional outcome (Glasgow Outcome Scale extended) at 6 months. Our secondary objectives are to evaluate the overall functional outcome, quality of life, psychological outcomes and mortality at 6 months. We hypothesize that a liberal transfusion strategy (triggered by Hb ≤ 100 g/L) improves outcomes compared to a restrictive strategy (triggered by Hb ≤ 70 g/L).

**Design:** We will conduct a multicentre pragmatic randomized open blinded-endpoint (PROBE) trial in acutely ill TBI patients.

**Population:** We will include 712 adult patients admitted to an intensive care unit (ICU) with an acute moderate or severe blunt traumatic brain injury and a Hb ≤ 100 g/L. We will exclude patients with no fixed address, who received a transfusion after ICU admission, who have contraindications or known objection to transfusions, have a GCS of 3 with bilateral fixed dilated pupils, are brain-dead, have active life-threatening bleeding with hemorrhagic shock or an active life-threatening bleeding requiring an urgent surgical procedure, or for whom a decision to withhold or withdraw life-sustaining therapies was made.

**Methods:** Patients will be randomly allocated to a liberal or a restrictive transfusion strategy. The allocated transfusion strategy will be applied from the time of randomization to death or discharge from the ICU. Daily data collection will be done and 6-month outcomes will be centrally evaluated.

**Relevance:** If our hypothesis is confirmed, the superiority of a liberal strategy will improve long-term outcomes for the most vulnerable trauma patients. Conversely, an absence of benefit will favour the adoption of a restrictive strategy given the transfusion costs and resources spent. From the patient’s perspective, regardless of the findings, our results will determine the most effective RBC transfusion management strategy to ensure the provision of high quality of care through the best available evidence.
# 2. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CCCTG</td>
<td>Canadian Critical Care Trials Group</td>
</tr>
<tr>
<td>CHU</td>
<td>Centre hospitalier universitaire</td>
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<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
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<tr>
<td>CO</td>
<td>Cardiac output</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CTRC</td>
<td>Canadian Traumatic brain injury Research Consortium</td>
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<tr>
<td>DO$_2$</td>
<td>Oxygen delivery</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
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<tr>
<td>EQ-5D-5L</td>
<td>EuroQol five dimensions questionnaire</td>
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<tr>
<td>FAQ</td>
<td>Frequently asked questions</td>
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<tr>
<td>FIM</td>
<td>Functional independence measure</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>InTBIR</td>
<td>International Initiative for TBI Research</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GOSe</td>
<td>Glasgow Outcome Scale Extended</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NINDS</td>
<td>National Institute of Neurological Disorders and Stroke</td>
</tr>
<tr>
<td>O$_2$</td>
<td>Oxygen</td>
</tr>
<tr>
<td>OHRI</td>
<td>Ottawa Hospital Research Institute</td>
</tr>
<tr>
<td>PaO$_2$</td>
<td>Arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>PbtO$_2$</td>
<td>Brain tissue oxygen tension</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>Patient health questionnaire</td>
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<tr>
<td>PIT-TBI</td>
<td>Clinical Outcomes and Predictors of PITuitary Disorders in Patients With Moderate and Severe Traumatic Brain Injury: the PIT-TBI Prospective Multicenter Pilot Cohort Study (NCT02480985)</td>
</tr>
<tr>
<td>Qolibri</td>
<td>Quality of life after brain Injury</td>
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<tr>
<td>RBC</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>REB</td>
<td>Research Ethics Board</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SaO$_2$</td>
<td>Arterial oxygen saturation</td>
</tr>
<tr>
<td>SbtO$_2$</td>
<td>Brain tissue oxygen saturation</td>
</tr>
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<td>TBI</td>
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<td>TBI-Prognosis</td>
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<tr>
<td>TRALI</td>
<td>Transfusion-related acute lung injury</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VO$_2$</td>
<td>Oxygen consumption</td>
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</table>
3. Introduction

3.1 Background

What is the problem to be addressed?
In Canada, traumatic injury costs more than heart disease and stroke\(^1\). Each year, 25,000 Canadians are hospitalized for a traumatic brain injury (TBI), by far the leading cause of permanent impairment and death in trauma\(^1,2\). Most trauma deaths are associated with brain injuries, and survivors are frequently left with severe permanent impairments, disabilities generating significant direct and indirect costs, and healthcare resource utilization. Mortality remains unacceptably high following severe TBI (30 to 50%)\(^3,4\), and one third of survivors suffer from severe neurological sequelae such as debilitating or neurovegetative states. TBI consumes significant healthcare resources, each victim representing a lifetime burden of $1 million\(^1,5\).

Current guidelines for the clinical management of brain injury are based on limited evidence\(^6\). Consequently, clinical practice is led by opinion leaders, is highly variable, and results in significant outcome differences across centres\(^4\). Traumatic brain injury has been identified as a major research priority by several healthcare organizations and granting agencies\(^7\), as well as by the US Department of Defense\(^8\), the Canadian Armed Forces and several sports organizations\(^9\). The global media coverage of Michael Schumacher’s traumatic brain injury is the public demonstration of enduring knowledge and public concern with respect to TBI\(^10\).

Over their intensive care unit (ICU) stay, most critically ill patients with TBI will develop anemia\(^11-13\). Since oxygen delivery to tissues is highly dependent on hemoglobin (Hb) levels, anemia may lead to decreased oxygen delivery to end organs, and especially to a traumatized and fragile brain. Current TBI management focuses on improving oxygen delivery including the optimization of patients’ hemoglobin (Hb) levels with red blood cell (RBC) transfusion\(^6\). In the general critically ill population, evidence supports a restrictive RBC transfusion strategy (no transfusion until Hb reaches a low level), and this strategy is being adopted in TBI. However, it may decrease oxygen delivery to a fragile brain that is vulnerable to secondary permanent insults. Therefore, a liberal transfusion strategy for critically ill TBI patients is advocated by many experts.

Why is the hemoglobin level important for the brain?
Oxygen consumption (VO\(_2\)) is dependent on oxygen delivery (DO\(_2\)). DO\(_2\) to any cell is dependent on the cardiac output (CO), dissolved oxygen in blood (SaO\(_2\) and PaO\(_2\)), and Hb concentration as per the following equation:

\[
DO_2 = (CO \cdot Hb \cdot O_2 \text{ saturation} \cdot 1.39) + 0.003 \cdot PaO_2
\]

Assuming normal cardiac function, and an adequate provision of oxygen in the blood (SaO\(_2\) and PaO\(_2\)), the only other way to improve oxygen delivery to the brain is by optimizing Hb concentration. However, oxygen delivery in the brain may also be dependent on other mechanisms. Like all cells in the body, oxygen is required to permit neuronal metabolism. However, the brain is different than most other organs as there are no anaerobic pathways that could compensate in suboptimal oxygenation states. While the cardiac output is a major variable of oxygen delivery in the rest of the body, it appears not to play a role in the brain as it does in other organs\(^14\). Instead, the cerebral blood flow (CBF) is one of the key elements in oxygen delivery to the brain cells:

\[
DO_2 = (CBF \cdot Hb \cdot O_2 \text{ saturation} \cdot 1.39) + 0.003 \cdot PaO_2
\]
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The cerebral blood flow is directly affected by the cerebral perfusion pressure and inversely by the cerebrovascular resistance. Complex autoregulation mechanisms based on metabolic, pressure, chemical and neural changes ensure appropriate oxygen delivery within a certain range of non-optimal physiological conditions\textsuperscript{15}.

**Are adaptive mechanisms affected in critically ill patients with TBI?**

Although adaptive mechanisms exist, cerebral autoregulation is disturbed in most critically ill patients with TBI, thus preventing adaptation to lower Hb levels\textsuperscript{16-19}. The variety of lesions caused by trauma, such as cerebral contusions, hemorrhage and edema, may impair cerebral autoregulation and the integrity of the blood brain barrier. The loss of integrity of the blood-brain barrier, whose function is to ensure protection of the brain from the many influences of the systemic blood circulation, further compromises the brain’s ability to adequately compensate for hypoxemia and amplifies its vulnerability to reduced oxygen states.

Clinical data supports the notion that RBC transfusion improves oxygen delivery to the human brain. In prospective observational studies in brain-injured patients, RBC transfusion has been shown to be associated with improved brain tissue oxygen measurements after RBC transfusion\textsuperscript{20,21}. Interestingly, using cerebral microdialysis in the same patients to measure markers of cerebral metabolism, no significant improvement in cerebral metabolism was observed after RBC transfusion. Such preliminary studies further support the equipoise regarding RBC transfusion in TBI, and raise the fundamental concern of the significance of such surrogate measures and their association or not with clinically significant outcomes in these patients.

**What is the current practice regarding RBC transfusion in TBI?**

Our CIHR-funded work has demonstrated that transfusion of RBCs is common in patients who have TBI across Canada, and that TBI severity is an important determinant of RBC transfusion\textsuperscript{22}. Importantly, our work has illustrated the absence of a consensus about the optimal strategy of RBC transfusion in TBI patients\textsuperscript{23}. We performed a pan-Canadian multicenter retrospective cohort study using administrative data (National Trauma Registry) to evaluate the frequency, determinants and outcomes associated with RBC use in critically ill patients with moderate or severe TBI using Canada’s national trauma registry (n=7062). We observed that 28% of patients were transfused with RBC at some point during their hospital stay\textsuperscript{24}. Using data from the Nova Scotia Trauma Registry and Lab and Pathology Central Database of the Queen Elizabeth II Health Sciences Centre, we also found considerable variation in transfusion practice with pre-transfusion Hb levels varying significantly within centres (median 81 g/L, IQR 67-100)\textsuperscript{25}. We also observed an increased risk of death with transfusion, although confounding by indication is likely present.

**3.2 Literature Review**

We conducted a systematic review of comparative studies to evaluate the effect of Hb level on various clinical outcomes in neurocritically ill patients\textsuperscript{23}. Six studies met inclusion and half of them had a high risk of bias. Data from these studies were not pooled given the heterogeneity observed in study designs and patient populations. Overall, no effect was observed on mortality, ICU length of stay, mechanical ventilation and multi-organ failure. Only one small randomized trial of 44 patients with aneurysmal subarachnoid hemorrhage was identified and failed to detect any differences in outcomes (adverse event and short-term functional outcome) in the 2 study groups (100 g/L compared to a threshold of 115 g/L)\textsuperscript{26}. This systematic review highlighted the paucity of comparative studies conducted to clarify the effect of transfusion or anemia in any neurocritically ill populations, particularly in TBI. It
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was conducted prior to a recent randomized controlled trial that evaluated the impact of erythropoietin and of RBC transfusion in TBI patients (2x2 factorial design)27. TBI patients broadly classified as “not following commands” were enrolled to either a trigger of 70 g/L or 100 g/L. While not confirming their hypothesis (superiority of the liberal arm), the study was not designed to look at a reasonable, physician supported, effect size (the study looked at a 50% improvement on the incidence of favourable outcome).

3.3 Rationale for the Trial
In view of extensive expert letters, attempts at consensus, editorials, and small underpowered clinical studies, little is known about the optimal transfusion strategies in this population. We recently conducted a systematic review of cohort studies and randomized controlled trials investigating the frequency of RBC transfusion, determinants and outcomes of RBC transfusion in TBI24. Data from 23 studies were pooled (n=7524), with a mean of 36% (95% CI 28 to 44%) of patients being transfused at some point during their hospital stay. Mortality was not significantly different between the 2 groups (transfusion vs. no transfusion), but an association was found between transfusion, lower admission GCS (mean difference: 1.38 points [95 % IC, 0.86-1.89]) and longer hospital length of stay (mean difference: 9.58 days [95 % IC, 3.94-15.22]). Hemoglobin thresholds to trigger transfusion were rarely described but varied greatly between studies (60-100 g/L), highlighting heterogeneous transfusion practices in the population of patients. We also conducted a systematic review of preclinical studies to evaluate the association between RBC transfusion strategies and important outcomes in animal models of acute cerebral injuries. We identified 6031 records and included 24 unique studies. We observed that data from animal studies are insufficient to inform transfusion practice in patients with acute cerebral injuries28.

Our work highlights the absence of high-quality evidence regarding the most effective RBC transfusion strategy to adopt in critically ill patients with TBI. Nonetheless, concerns regarding the use of a restrictive RBC transfusion strategy have been expressed by opinion leaders in the field. Some advocate that a liberal RBC transfusion strategy should be favoured considering the frailty of the brain to ischemia. Considering the persistent clinical equipoise and the paucity of data precluding the establishment of guidelines in this specific population, the uncertainty regarding optimal transfusion strategies in TBI, a large scale well-designed clinical trial is warranted to ensure evidence-base practice at the bedside.

4. Study Objectives

4.1 Primary Objectives
Our primary objective is to evaluate the effect of liberal (high Hb levels) vs. restrictive (low Hb levels) RBC transfusion strategies on patient-oriented neurological functional outcomes.

4.2 Secondary Objectives
Our secondary objectives are to evaluate the effect of transfusion strategies on overall functional outcome, quality of life, depression and mortality, and on the incidence of transfusion related complications.

4.3 Tertiary Objectives
Our tertiary objectives are to evaluate the effect of transfusion strategies on the incidence of infections, Hb levels, overall use of RBC transfusions, and ICU and hospital length of stay.
5. The Proposed Trial

5.1 Overall Trial Design
We will perform a pragmatic randomized open blinded endpoint (PROBE) trial that will compare the benefit of a liberal RBC transfusion strategy to a restrictive strategy on patient-oriented outcomes in critically ill patients with moderate or severe blunt TBI. We plan to recruit study participants in several Canadian level I and II trauma centres.

5.2 Study Population
5.2.1 Inclusion Criteria
We will include adult patients admitted to an ICU who have acute moderate or severe blunt TBI (Glasgow Coma Score \( \leq 12 \)) and Hb level \( \leq 100 \text{ g/L} \).

5.2.2 Exclusion Criteria
We will exclude patients with no fixed address, who received transfusion after ICU admission, who have contraindications or known objection to transfusions, who have a GCS of 3 with bilateral fixed dilated pupils, are brain-dead, have active life-threatening bleeding with hemorrhagic shock or requiring an urgent surgical procedure, or patients for whom a decision to withhold or withdraw life-sustaining therapies was made.

5.2.3 Identification of Potential Study Participants
A qualified Research Coordinator/Research Nurse at each centre will systematically screen all critically ill adult patients with TBI for eligibility on a daily basis. Critical care physicians, neurosurgeons, Site Investigators, trainees and nursing staff will be encouraged to refer patients. Information will be provided using a multifaceted approach to reach the medical team at the bedside (e.g., posters, in-person reminders). Potential study participants will be identified by the Research Coordinator/Research Nurse. We will use a deferred informed consent approach as we did in other transfusion trials in similar populations because we are studying a time-sensitive intervention (transfusion) that will most likely show benefit if implemented rapidly. Patients who are eligible for this trial are facing a life-threatening situation with high mortality risk. All eligible patients will have altered mentation and will be unable to provide informed consent for study enrolment. Legal next-of-kin are often not immediately available and it is impracticable to explain the study, receive consent and start the intervention in a timely manner. We will document excluded patients and determine their potential influence on the recruitment rate. We will also track eligible but non-enrolled patients to describe reasons for non-enrolment.

5.3 Time Window for Initiating the Study Intervention
Once the patient fulfills all inclusion criteria and no exclusion criteria, the study intervention will be initiated within 3 hours to avoid prolonged exposure to low Hb levels among patients assigned to the liberal strategy.

5.4 Randomization and Stratification Methods
Upon reaching a Hb \( \leq 100 \text{ g/L} \), eligible patients will be randomized (1:1 ratio) to either a liberal or restrictive transfusion strategy. Transfusion strategies were chosen based on available evidence, expert opinion, clinical equipoise, and the ability to ensure a significant separation of Hb levels between groups. We will use a central, concealed, computer-generated randomization process with variable permuted blocks of 4 and 6 and stratified by centre.
5.5 Trial Interventions

5.5.1 Intervention Group: Liberal Transfusion Strategy
Patients in this group will receive RBC transfusion if Hb ≤ 100 g/L. This threshold was selected because maintaining Hb levels greater than 100 g/L improves brain oxygenation.\(^9\) Observational studies in brain-injured adults have found that the brain tissue partial pressure of oxygen (PtO\(_2\)) is improved with higher Hb levels and, in most patients, increased with RBC transfusion\(^{21}\). In physiological studies performed in brain-injured patients (TBI and subarachnoid hemorrhage), a Hb level of 100 g/L and less was associated with metabolic distress measured by brain microdialysis and cerebral perfusion and brain tissue oxygenation (PtO\(_2\)) neuro-monitoring systems\(^{20,21,32}\). These studies were, however, not designed to find an association between Hb threshold and clinical outcomes. This threshold has been considered acceptable in a survey of clinicians who care for ICU patients with neurological injury\(^{33}\). The maximum threshold of Hb to trigger RBC transfusion in aneurysmal subarachnoid hemorrhage was 100 g/L. A transfusion trigger of 100 g/L and more has previously been shown to be acceptable in other neurocritically ill populations\(^{26}\). The use of this liberal threshold will also allow to clearly “separate” the groups (restrictive vs. liberal) with a significant difference in mean Hb levels.

5.5.2 Control Group: Restrictive Transfusion Strategy
Patients in this group will receive RBC transfusion only if Hb ≤ 70 g/L. We choose this threshold because it is the most studied restrictive RBC transfusion threshold in other critically ill populations and is widely accepted by bedside clinicians\(^{34,35}\). It is also an acceptable threshold for clinicians who care for brain-injured patients. In a survey of 312 intensivists, trauma surgeons and neurosurgeons practicing in level 1 trauma centres in the US, most respondents chose a threshold of 70 g/L or less as a trigger for transfusing patients with severe TBI and 55% preferred a restrictive transfusion strategy in patients with severe TBI and normal intracranial pressure\(^{36}\). Similar surveys in other neurocritically ill populations support the use of a comparable restrictive Hb threshold to trigger transfusion. Among those, in 531 practicing intensivists and neurosurgeons in North America, the lowest acceptable Hb threshold to trigger an RBC transfusion was 70 g/L in more than 70% of respondents caring for patients with aneurysmal subarachnoid hemorrhage\(^{33}\).

5.5.3 Protocol Violation
The following situations will be considered a protocol violation: 1) RBC transfusion occurring while the Hb threshold was not reached, 2) RBC transfusions occurring more than 3 hours after the Hb threshold is reached, and 3) transfusion of more than 1 unit without reassessing the Hb level. Protocol violations will have to be reported to the Method Centre within 72 hours.

5.5.4 Cointerventions
To promote uniform management among participating ICUs, standard therapeutic strategies will be recommended, but not protocolized, according to the Brain Trauma Foundation guidelines\(^6\). No interventions other than the allocated transfusion threshold will be protocolized.

5.6 Duration of Treatment Period
The treatment strategy will be applied until death or ICU discharge, whichever comes first. We will transfuse a single unit at a time when the Hb threshold is reached. Additional transfusions will be given if the post-transfusion Hb level remains below the assigned threshold. In both groups, RBC will be transfused as soon as possible but within 3 hours after the Hb threshold is reached.
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5.7 Participating Centres
Several Canadian level I and II trauma centres already committed to participating in the trial: Queen Elizabeth II Health Sciences Center (Halifax, Nova Scotia), CHU de Québec-Université Laval – Hôpital de l’Enfant-Jésus (Québec, Québec), CIUSSS du Nord de l’Île de Montréal - Hôpital du Sacré-Cœur de Montréal (Montréal, Québec), CIUSSS Mauricie-et-Centre-du-Québec (Trois-Rivières, Québec), CIUSSS de l’Estrie (Sherbrooke, Québec), Centre universitaire de santé McGill (Montréal, Québec), The Ottawa Hospital (Ottawa, Ontario), Sunnybrook Health Sciences Centre (Toronto, Ontario), St. Michael’s Hospital (Toronto, Ontario), Hamilton Health Sciences Centre (Hamilton, Ontario), London Health Sciences Centre (London, Ontario), Health Sciences Centre Winnipeg (Winnipeg, Manitoba), Foothills Medical Centre (Calgary, Alberta), University of Alberta Hospital (Edmonton, Alberta), Royal Alexandra Hospital (Edmonton, Alberta), and Vancouver General Hospital (Vancouver, British Columbia). Additional potential sites have been identified and should join the participating centres.

5.8 Eliminating Bias
We have implemented several strategies to reduce the risk of bias. First, we will use concealed randomization to avoid selection bias. Given the nature of the intervention and its effect on Hb levels, a double-blind design is impossible. However, we will comprehensively document co-interventions. We will standardize data collection by using electronic case report forms, comprehensive standard operating procedures, and publication of newsletters and study website updates to disseminate responses to FAQ. To minimize information bias, we have planned independent central blinded outcome assessment using standardized and validated instruments. We will also perform blinded statistical analyses. To limit losses to follow up, we will gather complete contact information for the patients, their family practitioners and their caregivers. Local Research Coordinators/Research Nurses will send personalized reminder letters and ensure phone call confirmation of upcoming interviews.

5.9 Recruitment Rate
We anticipate starting recruitment in Spring 2017. We plan a 3-month staggered start-up period, a 42-month recruitment period (average recruitment of 1 to 2 patients/centre/month), and a 6-month period for outcome assessment.

6. Patient Safety

6.1 Risks to the Safety of Participants Involved in the Trial
It is expected that patients in the liberal transfusion strategy arm will receive more RBC transfusions. However, both study arms are part of usual care in many centres and the research risk to participants is minimal. RBC transfusion strategy trials in other patient populations have been conducted with minimal risks.30,34,35

6.2 Serious Adverse Events
Our rationale for reporting serious adverse events (SAE) is in agreement with our statement on academic trials in critically ill patients.37 Several potential SAEs are already reported as outcomes, defined a priori, while other events are common expected ICU events. Potential SAEs not reported as study outcomes or that are not common ICU events, will be defined as any post-randomization adverse occurrence or event, or response to the study intervention, that requires inpatient hospitalization after discharge or prolongation of existing
hospitalization; that results in persistent or significant disability/incapacity; or that results in a congenital anomaly/birth defect; that is life threatening; that results in death. Any events that ICU physicians or Site Investigators label as unexpected will be described fully. These will be collated and submitted to the independent Data Safety Monitoring Committee (DSMC).

6.3 Removal of Study Participant
The study participant, their representatives and their most responsible physician, Site Local Investigators, the Executive Committee, the Research Ethic Boards, the DSMC and CIHR may stop study intervention if new discoveries or information suggest that pursuing study participation is not in the best interest of the study participant. In this situation, and in accordance with current regulation, we will pursue data collection unless consent is denied.

7. Data Collection

7.1 Data Collection

7.1.1 Frequency and Duration of Follow-Up
Study participants will be followed daily while in the ICU, at hospital discharge and at 6 months.

7.1.2 Baseline characteristics
Baseline characteristics will be collected by the study team at time of enrolment. We will record age, sex, comorbidities, home medications, mechanism and severity of TBI, extracranial injuries, score and Injury Severity Score\(^3\), the main findings on admission brain CT-Scan, the Marshall\(^3\) and the Rotterdam\(^4\) CT scores. We will also collect time from eligibility to randomization and from randomization to study intervention implementation.

7.1.3 Daily data during the ICU stay
Research Coordinators/Research Nurses at each site will prospectively collect clinical data (e.g. temperature, pupillary reflexes), episodes of hypoxemia ([oxygen saturation < 90% for ≥ 5 minutes] and hypotension [systolic blood pressure < 90 mm Hg for ≥ 5 minutes]), daily laboratory tests (e.g. blood count, glucose, arterial blood gases, serum sodium), and advanced neuromonitoring data for patients who have invasive devices (e.g. episodes of increased intracranial pressure [≥ 25 mm Hg for ≥ 5 minutes], cerebral hypoperfusion [cerebral perfusion pressure < 50 mm Hg for ≥ 5 minutes] and, if the case, invasive and/or non-invasive brain tissue oxygenation [brain tissue oxygen tension [PbtO\(_2\)] < 15 mm Hg for ≥ 5 minutes, and brain tissue oxygen saturation [SbtO\(_2\)] > 20% below baseline for ≥ 5 minutes or [SbtO\(_2\)] < 60% for ≥ 5 minutes]). These values correspond to the recommended treatment thresholds\(^6\).

We will capture the use of cointerventions (e.g. cerebrospinal fluid and hematoma drainage, decompressive craniectomy, therapeutic hypothermia, hyperosmolar therapy, sedatives, neuromuscular blockers, tranexamic acid, erythropoietin, use of other blood products, other surgical procedures) and the intensity of care (Therapy Intensity Level Score)\(^4\)\(^1\)-\(^4\)\(^3\). At ICU discharge, we will collect the length of stay and the duration of mechanical ventilation.

7.1.4 Hospital discharge
At hospital discharge, Research Coordinators/Research Nurses will collect the following data: 1) results of latest imaging (CT and MRI), 2) surgical procedures, infections and transfusion reactions that occurred during the hospital stay, 3) length of stay, 4) discharge status, 5) cause of death, 6) occurrence of brain death and 7) the reasons that motivated the withdrawal of life-sustained therapies.
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7.2 Monitoring of the Trial
The Method Centre and the Ottawa Hospital Research Institute (OHRI) data management services will periodically assess the data collected for accuracy and completeness, for study participant safety and benefit.

7.3 Storing and Archiving Data
Data will be kept for 10 years following the end of the trial. Source documents will be kept in each participating centres in locked filing cabinets and offices accessible by the Site Principal Investigators and their authorized personnel. Coded information will be entered in a web-based electronic database and stored at the central data warehouse of the OHRI. OHRI meets Health Canada recommendations and Good Clinical Practice for paper-based and electronic document control system. Personnel of the OHRI data management services and of the coordinating centre will have secured access to all study data.

8. Outcome Measurement
Our 6-month primary and secondary outcome measures are validated in TBI and aligned with the Common Data Elements recently developed by the National Institute of Neurological Disorder and Strokes (NINDS). All primary and secondary outcomes will be assessed centrally by trained research personnel blinded to the intervention. Six months is the standard timing of evaluation used in recent TBI trials and corresponds to the plateau phase of recovery.

8.1 Primary Outcome
We will measure the extended Glasgow Outcome Scale (GOSe) to assess neurological outcome at 6-month. The GOSe scale is valid, reliable and sensitive to change. It is the current gold standard clinical and patient-oriented outcome in this population, and is widely used in TBI trials. It comprises 8 ranking levels (1=death, 2=neurovegetative state, 3=lower severe disability, 4=upper severe disability, 5=lower moderate disability, 6=upper moderate disability, 7=lower good recovery, 8=upper good recovery).

8.2 Secondary Outcomes
We will assess ICU, hospital and 6-month mortality. At 6-month, we will measure the Functional Independence Measure (FIM). The FIM has been used for over 2 decades in TBI patients to assess their progression during rehabilitation. The scale is sensitive to change and evaluates the amount of assistance required to perform 18 basic daily activities (13 physical and 5 cognitive components). Each component is scored on a 7-point scale, with higher scores indicating a greater degree of independence. We will also evaluate the quality of life using the EQ-5D-5L (generic scale) and the Qolibri (TBI-specific scale) questionnaires. To evaluate depression, we will use the self-reported Patient Health Questionnaire (PHQ-9), which includes 9 items that assess the frequency of depressive symptoms in the past 2 weeks. We will finally assess return to work of each study participant and complications related to transfusion (e.g. TRALI).

8.3 Tertiary Outcomes
We will capture the number of RBC units transfused in the ICU, lowest daily Hb, infections, duration of mechanical ventilation, and length of stay in the ICU and the hospital.
9. Statistical Analysis

9.1 Sample Size Calculation
Our sample size is based on the proportion of patients with an unfavourable outcome (GOSe ≤ 4)\textsuperscript{45,48,49}. Assuming a 40% risk of unfavourable outcome in the restrictive group\textsuperscript{48,49}, a sample size of 712 patients will allow us to detect an absolute risk reduction of 10% with a power of 80% and a type I error of 5%. Our sample size is conservative as it is based on a simple dichotomous cut-off of unfavourable outcome. Based on estimates and simulated data, using a sliding dichotomy approach will increase our ability to observe the planned effect size with a 95% power.

9.2 Statistical and Analytic Plan
All analyses will be made according to the intention-to-treat principle and blinded to the intervention. All results will be reported using 95% confidence intervals. Patient characteristics will be presented with means, medians or proportion, as appropriate.

The primary outcome will be assessed using a Mantel Haenszel Chi-Square test stratified for TBI severity (moderate vs. severe) and presented as the absolute risk reduction of unfavorable outcome (GOSe ≤ 4), and using the sliding dichotomy approach to account for the whole ordinal scale. In the sliding dichotomy approach, the point of dichotomy of the GOSe varies according to the baseline prognostic risk. This approach has been advocated by several trialists\textsuperscript{57} and used in recent NINDS-funded trials to increase the ability to detect smaller effect size with similar power\textsuperscript{48,49}. We will assess the baseline prognosis risk with the externally validated CRASH prognostic model\textsuperscript{58}. Subjects will be split into 6 quantiles\textsuperscript{57,59} according to their baseline prognostic risk. Patients categorized in the worst predicted prognosis quantile will be considered to have a favourable outcome if the 6-month GOSe is ≥ 3. Patients categorized in the best prognosis quantile will be considered to have a favourable outcome if the 6-month GOSe is ≥ 8\textsuperscript{49}. We will also analyze the primary outcome using logistic regression analysis with adjustments for age, sex, pupillary reactivity to light (both, one, none), GCS, admission CT-Scan results\textsuperscript{58} (petechial hemorrhages, obliteration of the third ventricle or basal cisterns, midline shift, subarachnoid bleeding, non-evacuated hematoma), major extra-cranial injury and centres (random intercept).

Mechanical ventilation duration and length of stay will be compared using the Wilcoxon rank sum while the number of RBC units transfused and the lowest daily Hb will be compared using Student’s t test and general linear models, respectively. To assess the other outcomes, we will use multivariate linear regressions for continuous outcomes and multivariate logistic regression for dichotomous outcomes, adjusted for the same covariates as per the primary outcome analysis.

9.3 Subgroup Analyses
We will perform subgroup analyses according to age, sex, TBI severity, baseline TBI prognosis according to the CRASH prognosis model, presence of extracranial injury, time from TBI to randomization, comorbidities, transfusion prior to ICU admission, occurrence of events prior randomization such as decompressive cranectomy, evacuation of a mass lesion, episode of increased intracranial pressure, hypotension, hypoxemia, decreased cerebral perfusion pressure, decreased PbtO\textsubscript{2} and decreased SbtO\textsubscript{2}. 
A sensitivity analysis will be performed for deaths associated with the withdrawal of life-sustaining therapies.

9.4 Interim Analysis
We plan one interim analysis at 50% enrolment using the Haybittle-Peto criterion (p <0.001).

9.5 Loss to Follow-Up Rate
To limit losses to follow up, we will gather complete contact information for the patients, their family practitioners and their caregivers. Local Research Coordinators/Research Nurses will send personalized reminder letters and confirm upcoming interviews with study participants by phone. We will have flexible schedules for centralized outcomes assessment. We will obtain survival status of patients lost to follow up from provincial public registries. In our CIHR-funded multicentre TBI-Prognosis prospective cohort study, we had no lost to follow up at 6 months60.

9.6 Compliance
To promote protocol adherence, Site Research Coordinators/Research Nurses will report protocol violations to the Coordinating Centre within a 72-hour window. Reasons for non-adherence will also be recorded. The Coordinating Centre will provide rapid feedback to participating sites.

10. Trial Management

10.1 Method Centre
The Method Centre of the trial is the CHU de Québec–Université Laval. The Method Centre has a productive research team in critical care neurology and trauma (www.criticalcare-neurotrauma.ca). Our staff (team manager, study coordinator, research coordinators, research nurses, and research associates) has the experience in conducting CIHR-funded multicenter research. We work with the CHU Ste-Justine Research Centre to oversee part of the trial coordination and with the OHRI data management services to oversee the data management of the trial. The OHRI has experts in clinical trial design, data management and statistics and experience in supporting large multicenter trial. The central data warehouse using an electronic interface will be hosted at the OHRI. Data analysis will be performed at both the Method Centre and OHRI.

10.2 Principal Investigators and Site Investigators Roles
Site Research Coordinators/Research Nurses will ensure screening, recruitment, consent and data collection under the supervision of Site Principal Investigators and according to all statutes, regulations, rules, guidelines and laws mentioned in the inter-institutional study agreement.

10.3 Steering Committee
The trial will be overseen by a Steering Committee that will meet at least every 4 months during the conduction of the trial. The Steering Committee will comprise all Co-Investigators and Knowledge Users. This includes researchers with strong and extensive expertise in methods, in TBI and neurocritical care, neurosurgery, hematology, transfusion research, trauma, critical care and large-scale multicentre trials (see APPENDIX 1). Knowledge users from different organizations and their representatives are part of the steering committee.
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These organizations are the Institut national d’excellence en santé et service sociaux, Brain Injury Canada, Canadian Anesthesiologists Society, Canadian Blood Services, Canadian Critical Care Society and the Canadian Critical Care Trials Group. Critical care physicians and neurosurgeons are involved at each participating site.

10.4 Executive Committee
We have established an Executive Committee to address day-to-day clinical and methodological issues. The Executive Committee is composed of the 3 Principal Investigators (Alexis Turgeon, Dean Fergusson, François Lauzier). The Committee will meet with the Project Manager at least twice monthly. The Project Manager and a research assistant will be responsible for the coordination, the day-to-day proceedings and links with participating sites. They have experience in coordinating large multicentre trials in TBI and transfusion with our team. Specific expertise in blood transfusion will be provided ad hoc by 3 hematologists, both members of the Steering Committee, with expertise in blood bank management and transfusion (Vincent Laroche, Alan Tinmouth, Ryan Zarychanski). If needed, other expertise (e.g. trauma, neurosurgery, critical care) will be sought ad hoc among other Steering Committee members.

10.5 Data Safety and Monitoring Committee
We have adopted the Data Safety and Monitoring Committee (DSMC) charter template from the DAMOCLES Study Group. The charter will be reviewed and modified by the DSMC as necessary. Periodically, the DSMC will independently review reports received directly from the HEMOTION Method centre, including blinded SAE reports, protocol adherence, indicators of trial management (e.g. enrolment, consent). The DSMC will also blindly evaluate primary, secondary and tertiary outcomes at the interim analysis. The DSMC will maintain written records of all its meetings.

10.6 Canadian Critical Care Trials Group
The Trial will be conducted under the auspices of the Canadian Critical Care Trials Group (CCCTG). The CCCTG is an open membership group, inclusive of all healthcare professionals - physicians and health scientists, nurses, pharmacists and physiotherapists who care for critically ill patients. The mission of the CCCTG is to promote and assist in the implementation of investigator-initiated, patient-oriented, multicentre research. Several members of the Steering Committee and Site Principal Investigators are members of the CCCTG.

10.7 Canadian Traumatic Brain Injury Research Consortium
The Trial will also be conducted in collaboration with the Canadian Traumatic Brain Injury Research Consortium (CTRC). The CTRC is a CIHR funded network that was created to enhance collaborations among Canadian scientists working on different aspects of the continuum of care for traumatic brain injury patients. The CTRC encourages communication and collaboration between adult and pediatric scientists and between scientists working in basic, translational and clinical sciences. Several members of the Steering Committee and Site Principal Investigators are members of the CTRC.

11. Ethical Issues
11.1 Consent Process
We will obtain approval from the research ethics board (REB) prior to study initiation at each participating centre. The REB of the CHU de Québec - Université Laval will act as the main evaluating REB for the province of Québec, as per the provincial multicentre evaluation process. All patients with moderate to severe TBI will be temporarily unable to provide an informed consent. Initial consent will be sought from a surrogate decision maker. If no surrogate decision maker is present at the bedside, a deferred informed consent approach will be used and data collected. Should the patient regain capacity to consent, his/her consent to continue participation in the trial will be sought. It is expected that patients in the liberal transfusion strategy arm (100 g/L) will receive more RBC transfusions than patients randomized to the restrictive arm (70 g/L). However, both arms of the trial are part of usual care in many centres and the research risk to participants is minimal. RBC transfusion strategy trials in other patient populations have been conducted with minimal safety risks.

11.2 Confidentiality
Confidentiality will be maintained by coded identification, password protected files and websites, locked filing cabinets and offices. Direct identifiers will be removed from the information and replaced with a code. Local Principal Investigator will be able to re-identify specific participants. The code list will be kept in secured cabinets and offices at each participating site, accessible by the Site Principal Investigators and their authorized personnel. The central data warehouse at OHRI meets Health Canada recommendations and Good Clinical Practice for paper-based and electronic document control system. Personnel of the OHRI data management services will have secured access to all study data. The web servers and the database server are physically and virtually protected, and are located in the secured data centre of The Ottawa Hospital along with other clinical data servers as it follows the same privacy and security policies.
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12. References

2. Canadian Institute for Health Information. The Burden of Neurological Diseases, Disorders and Injuries in Canada. Ottawa, Canada 2007.
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APPENDIX 1. Members of the Steering Committee

Investigators

Turgeon, Alexis F. CHU de Québec-Université Laval, Québec (Québec)

Fergusson, Dean. Ottawa Hospital Research Institute, Ottawa (Ontario)

Lauzier, François. CHU de Québec-Université Laval, Québec (Québec)

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Ball, Ian. University of Western Ontario, London (Ontario)

Burns, Karen. Li Ka Shing Knowledge Institute, Toronto (Ontario)

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Moore, Lynne. CHU de Québec-Université Laval, Québec (Québec)

Riopelle, Richard. Brain Injury Association of Canada, Ottawa (Ontario)

Scales, Damon. Sunnybrook Research Institute, Toronto (Ontario)

Shahin, Jason. Université McGill, Montréal (Québec)

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Zygun, David. University of Alberta, Edmonton (Alberta)

Knowledge users

Canadian Anesthesiologists Society, Susan O’Leary, Past-President, Hamilton (Ontario)

Canadian Critical Care Trials Group, Paul Hébert, Chair, Montréal (Québec)

Canadian Critical Care Society, Alison Fox-Robichaud, Chair, Hamilton (Ontario)

Institut national d’excellence en santé et services sociaux, Julien Clément, Medical Advisor, Québec (Québec)

Héma-Québec, Gilles Delage, Vice-President of Medical Affairs – Microbiology, Montréal (Québec)