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Hemoglobin transfusion threshold in traumatic brain injury optimization (HEMOTION): a multicenter, randomized, clinical trial protocol

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is the leading cause of mortality and long-term disability in young adults. Despite the high prevalence of anemia and red blood cell (RBC) transfusion in TBI patients, the optimal hemoglobin (Hb) transfusion threshold is unknown. We undertook a randomized trial to evaluate whether a liberal transfusion strategy improves clinical outcomes compared to a restrictive strategy.

Methods and analysis: HEMOTION is an international pragmatic randomized open label blinded-endpoint clinical trial. We will include 742 adult patients admitted to an intensive care unit (ICU) with an acute moderate or severe blunt TBI (Glasgow Coma Scale [GCS] ≤ 12) and a Hb level ≤100 g/L. Patients are randomly allocated using a 1:1 ratio, stratified by site, to a liberal (triggered by Hb ≤100 g/L) or a restrictive (triggered by Hb ≤70 g/L) transfusion strategy applied from the time of randomization to the decision to withdraw life-sustaining therapies, ICU discharge, or death. Primary and secondary outcomes are assessed centrally by trained research personnel blinded to the intervention. The primary outcome is the Glasgow Outcome Scale extended (GOSe) at 6 months. Secondary outcomes include overall functional independence measure (FIM), overall quality of life (EQ-5D-5L), TBI specific quality of life (QOLIBRI), depression (PHQ-9) and mortality.

Ethics and dissemination: This trial is approved by the CHU de Québec—Université Laval research ethics board (MP-20-2018-3706) and ethic boards at all participating sites. Our results will be published and shared with relevant organizations and healthcare professionals.

Expected outcomes and significance: If a liberal transfusion strategy improves clinically important outcomes, we will recommend that it is rapidly implemented as a standard of care.

Otherwise, the use of a restrictive strategy will be justified and will allow preserving scarce resources, rationalizing health expenditures, and minimizing complications related to transfusion.

Trial registration number: ClinicalTrials.gov Identifier: NCT03260478.

STRENGTHS AND LIMITATIONS OF THIS TRIAL

- The multicenter international recruitment and our pragmatic approach will provide generalizable findings.
- The blinded outcome assessment will minimize ascertainment bias.
- The sample size and sliding dichotomy analysis will increase our ability to detect smaller effect size with similar power for a given population size.
- Transfusions administered as part of the initial resuscitation of acute trauma prior to ICU admission will not be protocolized.

INTRODUCTION

Traumatic brain injury (TBI) is a significant public health concern and represents the leading cause of mortality and long-term disability in young adults[1]. For these patients, the cerebral autoregulation that normally compensates for variations in oxygen delivery is impaired[2], rendering their brain vulnerable to ischemia and secondary injuries. In the absence of high-quality evidence, several experts have suggested maintaining higher hemoglobin (Hb) levels (>100 g/L) on the assumption that it reduces metabolic distress and improves brain tissue oxygenation[3-5]. The adoption of a liberal transfusion strategy has important resource implications since most patients with TBI will develop anemia[6] and approximately one third will be transfused during their hospital stay[7].

The evidence to support transfusion strategies in patients with TBI remains scarce. In a systematic review of studies in neurocritical care patients, we found insufficient evidence to support the use of a specific transfusion threshold to improve morbidity and mortality[8]. A recent randomized controlled trial showed no effect of RBC transfusion on neurological outcomes in patients with moderate or severe TBI, although the expected effect size was large and most patients included were not anemic[9]. To date, clinical practice guidelines are based on limited evidence and do not provide clear recommendations regarding RBC transfusion in TBI[10 11]. As a result, transfusion practices vary greatly within and between centres[12 13]; many clinicians extrapolate the evidence supporting the non-inferiority of a restrictive strategy in critically ill patients without TBI[14 15] while others advocate for a liberal transfusion strategy pending stronger evidence to support this practice[16].

In collaboration with the Canadian Critical Care Trials Group (CCCTG), the Perioperative Anesthesia Clinical Trials group (PACT) and the Canadian Traumatic Brain Injury Research

Consortium (CTRC), we designed the HEMOTION (**HEMO**globin **T**ransfusion Threshold in Traumatic Brain **I**njury Optimizati**ON**) trial. The primary objective of our international pragmatic randomized open label blinded-endpoint (PROBE)[17] trial is to evaluate whether a liberal (higher Hb threshold) vs. a restrictive (lower Hb threshold) RBC transfusion strategy improves neurological outcomes in anemic moderate and severe TBI patients admitted to the intensive care unit (ICU). Secondary objectives will evaluate the effect of transfusion strategies on functional outcome, quality of life, depression, and mortality. Tertiary objectives will evaluate the effect of transfusion strategies on the incidence of transfusion-related complications, infections, Hb levels, number of RBC units transfused, and ICU and hospital length of stay. Herein, we report the trial protocol according to the SPIRIT statement[18]. This trial is registered with ClinicalTrials.gov (Identifier: NCT03260478).

METHODS AND ANALYSIS

Trial Settings and Eligibility Criteria

The HEMOTION trial is being conducted in level 1 and level II trauma centres in Canada, the United Kingdom, Brazil and France since September 2017. We are recruiting adult patients (≥18 years-old) admitted to the ICU with an acute (hospital admission within 24 hours of injury) moderate or severe (Glasgow Coma Score [GCS] ≤12)[19] blunt TBI and a Hb level ≤100 g/L. We exclude patients who receive transfusion after ICU admission, have contraindications or known objection to transfusions, or have no fixed address. We also exclude patients who meet the criteria for neurological determination of death, those with a GCS of 3 in combination with bilateral fixed dilated pupils, those with active life-threatening bleeding associated with hemorrhagic shock, and patients for whom a decision to withhold or withdraw life-sustaining therapies has been made at

the time of screening. Patients who received transfusion prior to ICU admission (e.g., in the emergency room or in the operating room), as part of the initial acute trauma resuscitation, are eligible. Research coordinators at each participating site screens daily all critically ill adult patients with TBI to determine eligibility. Table 1 depicts the schedule of interventions, data collection and outcome assessments. In the final report, we will report excluded patients and reasons for non-enrollment using the CONSORT flow diagram[20] (Figure 1).

Assignment of Interventions

Upon reaching a Hb ≤ 100 g/L and after a site investigator confirms eligibility, the research coordinator uses a secure, web-based, central, concealed, computerized randomization portal to allocate patients in a 1:1 ratio to either a liberal (experimental) or a restrictive (control) RBC transfusion strategy. Randomization is done with variable permuted blocks of 4 and 6, stratified by site. Staff members of the methods centre of the Ottawa Health Research Institute (OHRI) who are not involved in trial implementation generated the randomization sequence.

Interventions

Once randomized, the trial intervention is initiated within three hours in patients meeting the threshold for transfusion in their respective group to avoid prolonged exposure to Hb levels below this threshold.

Experimental Intervention: Liberal Transfusion Strategy

Patients in the liberal transfusion strategy group receive an RBC transfusion if their Hb is ≤100 g/L. This threshold, shown to be effective in maintaining adequate cerebral oxygenation[3-5],

is considered acceptable by clinicians caring for critical care patients with neurological injuries[16 21].

Control Intervention: Restrictive Transfusion Strategy

Patients in the restrictive transfusion strategy group receive an RBC transfusion only if their Hb is ≤70 g/L. We have chosen this threshold because it is the most studied restrictive RBC transfusion threshold[14 15] and reflects the current standard of care in non-bleeding critically ill patients without neurological or coronary artery diseases[11]. It also is a frequently used and accepted threshold for clinicians who care for brain-injured patients[16].

Duration of Treatment

The allocated transfusion strategy is applied throughout the ICU stay until ICU discharge, death, or a decision to withdraw life-sustaining therapy is made, whichever comes first. The study procedures are also implemented in the operating room, provided the patient is still admitted to the ICU. A single unit at a time is transfused when the Hb threshold is reached unless there is an active and uncontrolled bleeding requiring urgent care. Additional RBC transfusions are given if the post-transfusion Hb level remains below the assigned threshold. In both groups, RBCs are transfused within three hours after the Hb transfusion threshold is reached.

Compliance

Potential protocol deviations and violations are reported to the Coordinating Centre within 72 hours and further classified into four categories (Figure 2), reflecting the following situations wherein: i) an RBC transfusion occurred while the Hb threshold is not reached, ii) more than one unit is transfused without reassessing the Hb level between transfusions, iii) the delay between reaching the transfusion threshold and transfusion is greater than three hours or a transfusion never

occurred despite reaching the transfusion threshold, and iv) no transfusion occurred in the context of life-sustaining therapy withdrawal. Using a standard operating procedure, an adjudication committee will determine whether each reported event represents a protocol violation, a protocol deviation, or neither (see Appendix 1).

Cointerventions

No intervention other than the allocated transfusion threshold is protocolized. Standard therapeutic strategies according to the Brain Trauma Foundation guidelines are recommended[10].

Outcome Measures

Our primary and secondary outcome measures are validated in TBI patients and aligned with the Common Data Elements developed by the National Institute of Neurological Disorder and Strokes (NINDS)[22]. All primary and secondary outcomes are assessed centrally by trained research personnel blinded to the intervention to minimize the risk of bias during data collection. We chose a 6-month assessment as it is the most common time frame used in modern TBI trials and corresponds to the plateau phase of recovery[23]. Tertiary outcomes are assessed at participating sites, using standardized definitions (see Appendix 2).

Primary Outcome

We are using the Glasgow Outcome Scale extended (GOSe) to assess neurological outcome at six months[24]. The GOSe scale is reliable, sensitive to change[25 26], and is the most widely used clinical and patient-oriented outcome in this population[27-31]. It comprises eight ranking levels from 1 (death, least favorable outcome) to 8 (upper good recovery, most favorable outcome).

Secondary Outcomes

We are assessing ICU, hospital and 6-month mortality. At six months, we measure the Functional Independence Measure (FIM)[32]. The FIM has been used for over three 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 five cognitive components)[33 34]. Each component is scored on a 7-point scale, with higher scores indicating a greater degree of independence. We also evaluate the quality of life using the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) (generic scale) and the Quality of Life after Brain Injury (QOLIBRI) (TBI-specific scale) questionnaires[35-37]. To evaluate depression, we use the self-reported Patient Health Questionnaire (PHQ-9), which includes nine items that assess the frequency of depressive symptoms in the past two weeks[38].

Tertiary Outcomes

We are capturing the number of RBC units transfused in the ICU, lowest daily Hb, infections, duration of mechanical ventilation, and ICU and hospital length of stay. We are also assessing complications related to transfusion.

Data Collection

At enrollment, the study team collects baseline characteristics, pre-randomization cointerventions and episodes of secondary cerebral injury, which are defined as thresholds at which therapeutic intervention is recommended by practice guidelines[10] (see Table 1 and 2). We also collect time from eligibility to randomization and from randomization to study intervention implementation. Daily, we collect data on secondary injury episodes and cointerventions. At ICU discharge, we collect the length of stay and the duration of mechanical ventilation. At hospital discharge, we collect non-neurosurgical procedures, infections and transfusion reactions that occurred during the

hospital stay, as well as the reports of the brain imaging (computerized tomography [CT] and magnetic resonance imaging [MRI]), length of stay, discharge status and location, documentation of prognostic assessment, justifications provided by clinicians for discontinuing life-sustaining therapies, and occurrence of death by neurological criteria.

Table 1. Schedule of enrollment, interventions, data collection and outcome assessments

	Trauma	ICU	Hospital	6 months
Enrollment				
Eligibility screen		✓		
Informed consent		✓		
Allocation		✓		
Intervention – transfusion strategy				
Liberal (Hb > 100 g/L) or restrictive (Hb > 70 g/L)		✓		
Pre-randomization Data Collection*				
Demographics	✓			
Trauma characteristics	✓			
Physical examination	✓	✓		
Laboratory results	✓	✓		
Secondary insults	✓	✓		
Cointerventions	✓	✓		
Neurosurgical and non-neurosurgical interventions	✓	✓		
Blood product transfusions	✓	✓		
Transfusion reactions	✓	✓		
Daily Data Collection				
Physical examination		✓		
Laboratory results		✓		
Secondary insults		✓		
Cointerventions		✓		
Neurosurgical and non-neurosurgical interventions		✓		
Blood product transfusions		✓		
Transfusion complications	✓	✓		
Protocol deviation/violation		✓		
Trial outcomes				
Primary outcome				
Glasgow Outcome Scale extended				✓
Secondary outcomes				
Mortality		✓	✓	✓
Functional Independence Measure				✓
EuroQoL 5-Dimension 5-Level				✓
Quality of Life after Brain Injury (QOLIBRI)				✓

Patient Health Questionnaire-9				✓?
Transfusion complications		✓?		
Tertiary outcomes				
Red blood cells transfusion		✓?		
Lowest Hb		✓?		
Infections		✓?		
Length of mechanical ventilation		✓?		
Length of stay		✓?	✓?	

*Performed retrospectively after randomization. Hb, hemoglobin.

Table 2. Secondary cerebral injury definitions

	Definition
Hypoxemia	Oxygen saturation < 90% for ≥ 5 minutes on pulse oximetry
Hypotension	Systolic blood pressure < 90 mm Hg for ≥ 5 minutes
Intracranial hypertension	Intracranial pressure > 25 mm Hg for ≥ 5 minutes
Brain tissue hypoxia	Brain tissue oxygen tension [$PbtO_2$] < 15 mm Hg for ≥ 5 minutes *or* Brain tissue oxygen saturation [$SbtO_2$] > 20% below baseline for ≥ 5 minutes *or* $SbtO_2$ < 60% for ≥ 5 minutes

To limit loss to follow up, we are gathering complete contact information for patients, their family practitioners, and caregivers. Local research coordinators send personalized reminders and confirm upcoming interviews with patients. We use flexible schedules for centralized outcomes assessment. We obtain survival status of patients lost to follow-up from public registries or by reaching the primary care team. In our previous multicenter TBI-Prognosis prospective cohort study, we had no losses to follow-up at six months using those strategies[39].

Data Management

The HEMOTION Coordinating Centre, located at the *CHU de Québec-Université Laval Research Centre* (Québec City, Québec, Canada) oversees the trial coordination. Source documents are kept

at each participating site in locked filing cabinets and offices accessible by the site investigators and their authorized personnel. Coded information is entered in a web-based electronic database and stored at the Ottawa Methods Center at OHRI, which meets Health Canada recommendations and Good Clinical Practice for paper-based and electronic document control system. OHRI personnel have secure access to all trial data, but staff from the Coordinating Centre remain blinded to the intervention allocation.

Sample Size

Our sample size was calculated based on the proportion of patients who will experience an unfavorable outcome (GOSe ≤4)[24 27 28]. Assuming a 40% risk of unfavorable outcome in the control group[27 28], 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 1 error of 5%. Our sample size is conservative as it was based on the simple dichotomous cut-off and most used definition of an unfavorable outcome in TBI using the GOSe. Based on simulated data, a sliding dichotomy approach will increase our ability to observe the planned effect size with 95% power. To account for an estimated 2% dropout rate (consent withdrawals and losses to follow-up) based on observed aggregate rates at the interim analysis, the final sample size was increased to 742[40].

Statistical Methods

All analyses will be performed according to the intention-to-treat principle by biostatisticians blinded to the intervention and reported using 95% confidence intervals. Patient characteristics will be presented with means, medians or proportions, as appropriate. The primary outcome will be presented as quantile-specific odds ratios using a sliding dichotomy approach to account for the

whole ordinal scale. With the sliding dichotomy approach, the point of dichotomy of the GOSe for an unfavorable outcome varies according to the baseline prognostic risk. This approach has been advocated by several trialists[41] and used in recent TBI trials to increase the ability to detect smaller effect size with similar power[27 28]. We will assess the baseline prognosis risk with the externally validated International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model, which includes admission characteristics (hypoxemia, hypotension, and CT scan and laboratory results)[42]. Patients will be split into a minimum of three quantiles according to their baseline prognostic risk. Patients categorized in the worst predicted prognosis quantile will be considered to have an unfavourable outcome if the 6-month GOSe is ≤ 3 (i.e., death, vegetative state, or lower severe disability). We will use multiple imputation to simulate missing data values using imputation models for independent variables in respective analysis models with the number of imputations corresponding to the fraction of missing data, in line with recommendations[43].

We will perform the following secondary analyses for the primary outcome: per protocol analysis, best case-worst-case scenarios for patients with missing primary outcome, proportional odds analysis (provided the distribution of the GOSe meets the proportional odds assumption[44]), and analysis of the GOSe as a binary variable (GOSe ≤4 vs. > 4) using a Chi-Square test and multivariate logistic regression. In sensitivity analyses, we will compare results generated using multiple imputation to complete case results.

Duration of mechanical ventilation and length of stay will be compared using Cox shared frailty regression to account for the competing risk of mortality[45]. Other secondary outcomes including,

the number of RBC units transfused and the lowest daily Hb, will be compared between groups using generalized linear models with appropriate link functions and conditional distributions.

Subgroup Analyses

We will perform subgroup analyses for our primary outcome according to age, sex, TBI severity (moderate vs. severe), country, presence of heart disease, occurrence of decompressive craniectomy or surgical drainage prior to randomization, and occurrence of transfusion prior to ICU admission. We will use the Instrument to assess the Credibility of Effect Modification ANalyses (ICEMAN) to judge the credibility of apparent effect modification among subgroups[46].

Data Safety and Monitoring

We adopted the Data Safety and Monitoring Committee (DSMC) charter template from the DAMOCLES Study Group (see Appendix 3)[47]. The DSMC includes an international expert in transfusion medicine, a senior biostatistician and epidemiologist, and a neurologist with expertise in neurocritical care. Periodically, the DSMC will independently review reports received directly from the Ottawa Methods Centre, including blinded serious adverse events (SAE) reports, protocol adherence, indicators of trial management (e.g., enrollment, consent). The DSMC will also blindly evaluate the primary outcome at the interim analysis of 50% enrollment using the Haybittle-Peto criterion ($p < 0.001$)[48 49].

Serious Adverse Events

Our rationale for reporting SAE is in agreement with a statement on academic trials in critically ill patients[50]. Several potential SAEs are already reported as outcomes, defined *a priori,* while other

events are commonly 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 that is determined to be directly attributable 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 event that ICU physicians or site investigators label as unexpected will be described fully. These will be collated and submitted to the DSMC.

Data Monitoring

The HEMOTION Coordinating Centre team verifies data entered for completeness and accuracy (e.g., range checks for data value), generate queries and communicate with the sites as required. The frequency of the verifications depends on the site enrollment rates, with high enrolling sites having more than one monitoring visit. We are conducting remote continuous monitoring activities, including monitoring visits (remotely or on-site if required), and will perform a final closeout virtual visit for each site.

Patient and Public Involvement

Representative from Brain Injury Canada, a non-governmental organization whose vision is to promote a better quality of life for people affected by acquired brain injury[51], were involved in the trial design, and are involved in its conduction. Patient and caregiver engagement ensures that our study objectives are tailored to their needs.

Trial Oversight

The HEMOTION Steering Committee is comprised of co-investigators with expertise in TBI and neurocritical care, neurosurgery, hematology, transfusion research, trauma, critical care and large-scale multicentre trials. Knowledge users from various organizations and their representatives are also part of the Steering Committee. These organizations are the *Institut national d'excellence en santé et service sociaux*, Canadian Anesthesiologists Society, Canadian Blood Services, and Brain Injury Canada. We have established an Executive Committee to address day-to-day clinical and methodological issues. The Executive Committee is composed of the three principal investigators and is supported by the project manager and trial coordinator. The HEMOTION trial is being conducted under the auspices of the CCCTG, an inclusive group of healthcare professionals that promotes and assists in the implementation of investigator-initiated, patient-oriented, multicentre research in critically ill patients. The trial is also conducted in collaboration with the Canadian Perioperative Anesthesia Clinical Trials Group and the Canadian Traumatic Brain Injury Research Consortium that was created to enhance collaborations among Canadian scientists working in anesthesiology and perioperative medicine, and on different aspects of the continuum of care of TBI patients, respectively.

ETHICS AND DISSEMINATION

Research Ethics Approval and Consent Process

We obtained approval from the research ethics board prior to the initiation of the trial at each participating centre. Since all TBI patients are temporarily unable to provide an informed consent, initial consent is sought from a surrogate decision maker (see Informed Consent Form in Appendix 4). If a surrogate decision maker is not available, a deferred informed consent approach is used

where authorized by the local research ethics board as the research risk to patients is minimal, and the studied transfusion strategies are part of usual care in many centres[12 13] and considered acceptable by clinicians caring for these patients[16 21]. A deferred consent approached has been previously used in RBC transfusion strategy trials with no safety issues[52 53]. Should the patient regain capacity to consent, the consent to continue participation is sought. If the study intervention is suspended for any reason, we pursue data collection unless consent is denied.

Protocol Amendments

All past and future changes to the protocol are approved by research ethics committees prior to implementation. Shortly after the ethics approval was obtained and recruitment began, we amended the protocol to detail one exclusion criteria, modify the size of the permuted blocks used for randomization, specify the number of interim analyses, and shorten the time frame to report protocol violation to the Coordinating Centre (Appendix 5). In the spring of 2022, we implemented additional amendments and increased the sample size to compensate for post-randomization exclusions, consent withdrawals and losses-to-follow-up observed at the interim analysis. We detailed the adjudication process for protocol deviations and violations, corrected some administrative details (number of participating sites and countries, updated references), and modified the prognostic model to be used in the sliding dichotomy analysis.

Confidentiality

Confidentiality is maintained by coded identification, password protected files and websites, locked filing cabinets and offices. Direct identifiers are removed and replaced with a code. Site investigators can re-identify specific patients, if required by authorized persons. The code list is

kept in secured cabinets and offices at each participating site, only accessible by the site investigators and their authorized personnel. Electronic data are physically and virtually secured in the data centre physically located at OHRI.

Dissemination

The findings from this trial will be shared with relevant brain injury organizations and healthcare professionals, through the publication of manuscripts, conference presentations and seminars. Based on the findings, this trial will engage knowledge translation specialists to build an implementation strategy to reach as many stakeholders and members of the medical community as possible, to help reduce transfusion-related practice variation and thereby promote better outcomes for patients with TBI.

Current Trial Status

Recruitment began in September 2017 at the *CHU de Québec—Université Laval* and is currently ongoing at 34 recruiting sites in Canada, the United Kingdom, Brazil and France. The recruitment was initially planned to end in spring 2021. As of March 2022, 75% of the target sample size was achieved. Due to the COVID-19 pandemic and the increase of the sample size, the recruitment is expected to be completed in winter 2023.

CONCLUSION

The HEMOTION multicentre randomized controlled trial is evaluating the effectiveness of two common RBC transfusion strategies in critically ill patients with moderate or severe blunt TBI. If, as hypothesized, a liberal RBC transfusion strategy improves clinically important outcomes, it will

become standard practice and improve care. If a liberal RBC transfusion strategy is not shown to be superior to a restrictive strategy, the use of a restrictive strategy will then be justified to preserve scarce resources, rationalize health expenditures, and reduce complications related to transfusion. Our results will help clinicians to make informed evidence-based decisions regarding the use of the optimal RBC transfusion strategy to treat this specific patient population.

Authors' contributions:

AFT, DAF, and FLAU originally designed the trial. All authors contributed to the trial protocol. LC and MPP drafted the study implementation documents. AFT, DAF, and FLAU developed the statistical analysis plan. AFT, FLAU, MPP, LC and OC drafted the protocol manuscript. All authors read, edited and approved the final version of the manuscript.

Competing interests:

None declared.

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Figure 1. Flow Diagram

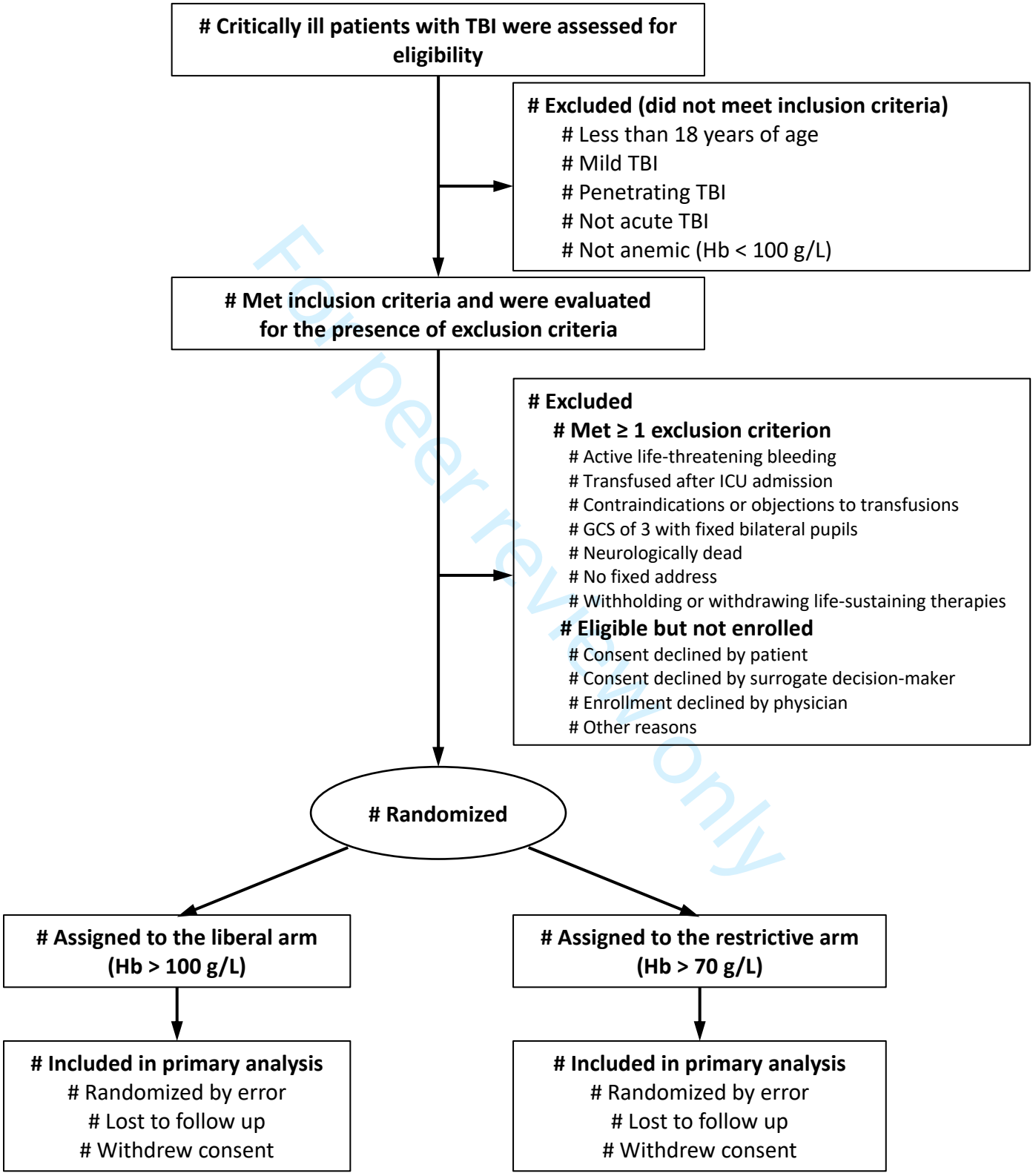
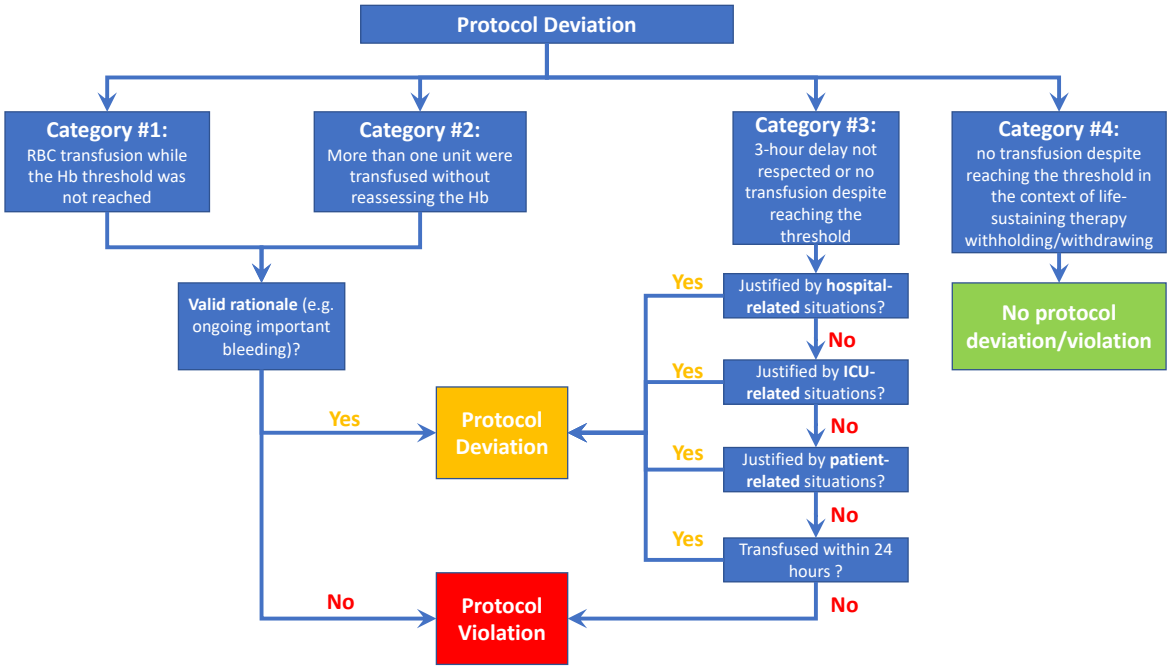


Figure 2. Potential Protocol Deviations and Violations



Appendix 1. Protocol violation adjudication process

Introduction

Adjudication in clinical trials is intended to minimize subjective decisions and systematic errors in the assessment of key information such as patient eligibility, study outcomes and protocol adherence. Evaluating protocol adherence is an important methodological aspect of conducting clinical trials as non-adherence can bias findings. Non-adherent participants may have an inherently different prognosis or be less likely to benefit from (or be harmed by) the study intervention than adherent participants because of suboptimal/sub or supratherapeutic exposure.

No clear, standardized or universal definition of protocol adherence is accepted. As a result, investigators must tailor methods for assessing protocol adherence to the specific characteristics of their trial. This is particularly challenging when the intervention to be tested is complex or involves complex participants and settings such as critically ill patients.

In trials evaluating different hemoglobin (Hb) transfusion thresholds, a clinically significant difference of Hb levels between groups throughout the duration of the intervention is an important objective to demonstrate the fidelity of the interventions and may be considered as the ultimate and true measure of protocol adherence. Since a definitive conclusion on the Hb level difference between groups can only be made at the end of the study, investigators have to monitor, while conducting the study, different parameters to ensure overall adherence.

One critical parameter of protocol adherence is adherence to the transfusion threshold. However, transfusion thresholds need to be contextualized and adapted to the clinical environment, keeping in mind that not all situations in which the transfusion threshold is not respected can be seen as clinically important protocol violations that may bias the results and expose study participants to unnecessary risks. For example, to suspend transfusion in patients for whom a decision to withdraw life-sustaining therapies has been made should not be seen as a protocol deviation or a protocol violation as it represents a judicious use of scarce resources that is unlikely to bias the results.

Some protocol violations are unlikely to have the same impact in a given situation depending on whether it occurs in one study group or another. As an example, transfusing red blood cells (RBC) to a patient allocated to the liberal group while not reaching the transfusion threshold does not have the same impact as transfusing a patient in the restrictive group who did not reach the transfusion threshold. The former situation would result in a greater separation of the Hb curves between study groups while the later would do the opposite. On the opposite, not transfusing a patient of the liberal group who reached the transfusion

threshold would attenuate the difference of the Hb level curves between study groups, while not transfusing a patient allocated to the restrictive group would accentuate this difference.

Another parameter that may be monitored in transfusion threshold trials is the time between reaching the transfusion threshold and administration of the transfusion itself. In patients with traumatic brain injury, the underlying hypothesis of aiming for higher Hb levels is that the injured brain is particularly sensitive to ischemia. Therefore, minimizing the exposure time to low Hb levels may increase the benefits (if any) of targeting higher Hb levels. However, several clinical situations can delay transfusion, such as hospital-related (e.g., rationalization of blood bank services outside of business hours, institutional policy on Hb validation for transfusion), ICU-related (e.g., rationalization of some interventions overnight), or patient-related factors (e.g., difficult crossmatch). These factors are important and may vary across centres, especially in trials conducted in various jurisdictions.

In HEMOTION, we advocate a pragmatic approach where any deviation from the protocol will not be systematically classified as a protocol violation. Instead, deviations will trigger a rigorous and transparent adjudication process whose goal is to systematically assess if each deviation was truly avoidable or clinically important.

Protocol deviations

Protocol deviations will be classified into three categories for review by the adjudication committee:

1. Any situation where RBC transfusion occurred while the Hb threshold was not reached.

2. Any situation where more than one unit were transfused without reassessing the Hb level between transfusion.

3. Any situation where there delay between the Hb measurement and the RBC transfusion is greater than 3 hours or where an RBCs were not transfused despite reaching the transfusion threshold.

If a transfusion is suspended in the context of life-sustaining therapies withholding or withdrawal, this will not be considered as a protocol deviation or violation.

Adjudication process

The protocol violation adjudication committee will consist of two of the principal investigators and three other coinvestigators, including one blood banker, one anesthesiologist and one intensivist. The information to adjudicate the protocol deviations will be extracted from the protocol deviation form. If necessary, additional information will be obtained directly from the research team as per requested by the adjudication committee. We will perform a calibration exercise to reduce the variability in assessments among raters. Independently, all five

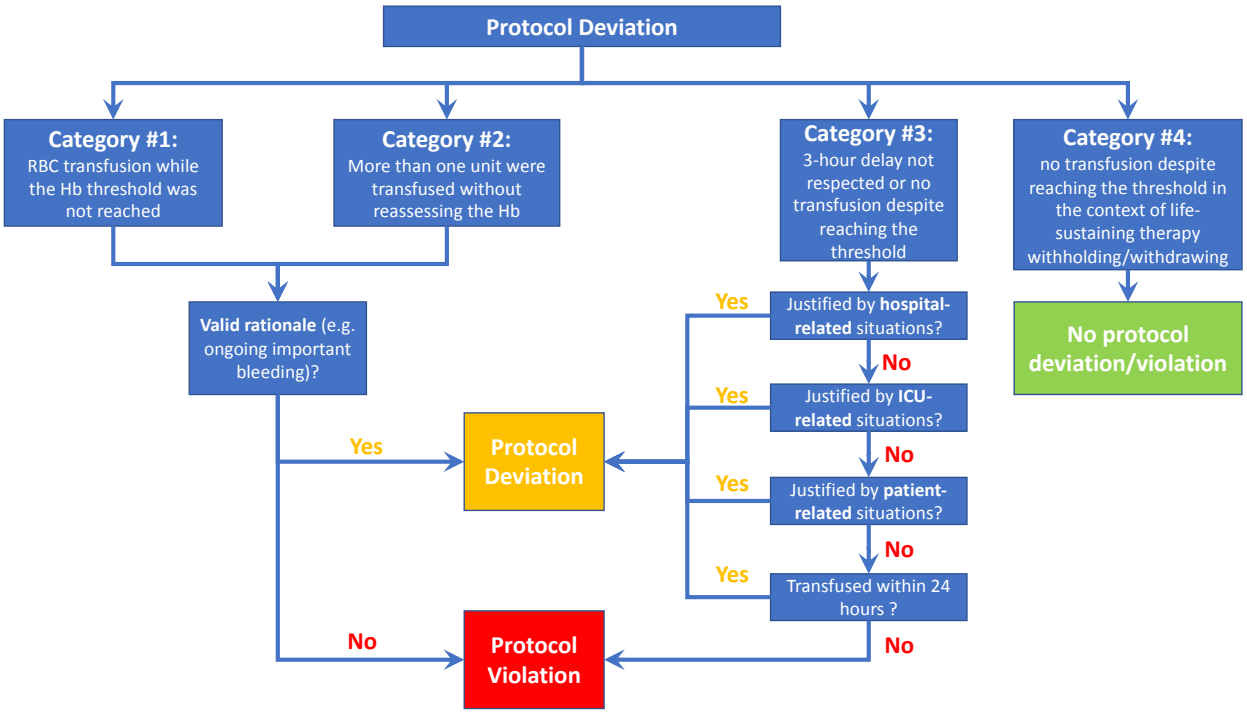
adjudicators will examine 20 *protocol deviations*, including at least three in each of the three above-mentioned deviation category (if the number of deviations per category is sufficient). Adjudicators will discuss their assessments and reasons for disagreement to attempt clarifying the adjudication process. Then, another set of 20 deviations will be evaluated. If the agreement for this set is excellent (kappa greater than 0.8), we will proceed with pairwise adjudication for the remainder of the trial. A pair of adjudicators, including at least one of the principal investigators, will independently assess each event. One of the two principal investigators will be randomly assigned to each deviation and paired with a randomly selected second adjudicator. All adjudicators will be independent and blinded to each other for their initial assessment. Disagreements between pairs of adjudicators will be resolved by further discussion and/or consultation with a third reviewer.

Definition of a protocol violation (see Figure 1)

1. Protocol deviations in which RBC transfusion occurred while the Hb threshold was not reached (**category #1**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or imminent or anticipated Hb drop below the transfusion threshold (e.g., Hb near the transfusion threshold and upcoming major surgery with high risk of bleeding). Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
2. Protocol deviations in which more than one unit were transfused without reassessing the Hb level between transfusion (**category #2**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or extremely low Hb levels. Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
3. Protocol deviations in which the three-hour delay between an RBC transfusion and the Hb measurement is not respected will remain classified as a protocol deviation if a valid rationale is provided to justify the delay. Valid justifications can be classified into three different categories (hospital-related, ICU-related, patient-related) and may include (without being limited to) the following scenarios:
    a. Hospital-related situations: rationalization of blood bank services outside of business hours, unavailability of blood due to orange code.
    b. ICU-related situations: rationalization of some interventions overnight due to limited staff issues, another more unstable patient requiring care, institutional policy on Hb validation for transfusion.
    c. Patient-related situations: difficult crossmatch, no IV access available.

    Subsequently, all transfusion delays that are not justified by either those three categories will be reclassified as a protocol violation only if the delay is greater than 24 hours.

Figure 1.



Appendix 2. Tertiary outcomes definition

Acute respiratory distress syndrome: Defined based on degree of hypoxemia: mild (200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg), moderate (100 mm Hg < $PaO_2/FIO2$ ≤ 200 mm Hg), and severe ($PaO_2/FIO2$ ≤ 100 mm Hg).

Congestive Heart failure (CHF): A documented history of CHF and medications for the treatment of CHF, such as diuretics (i.e., furosemide (Lasix™), +/- ACE inhibitors (i.e., ramipril (Altace™), etc.), or angiotensin 2 receptor blocker (i.e., losartan). Note that the use of these drugs does not necessarily mean that the patient has CHF.

ST elevation MI (STEMI): MI patient with chest discomfort or other ischaemic symptoms that develop ST elevation in two contiguous leads on ECG.

Non-ST elevation MI: MI patient with chest discomfort or other ischaemic symptoms without ST elevation in two contiguous leads on ECG.

Pneumonia (includes hospital-acquired pneumonia and Ventilator associated pneumonia): Definite infection (radiographic evidence of pulmonary abscess and positive needle aspirate OR histological proof on open lung biopsy or at post mortem), probable infection (positive culture of a pathogen known to cause pneumonia from a sputum or endotracheal aspirate specimen, from bronchial washings, bronchoalveolar lavage or bronchoscopy (regardless of quantitation)), possible infection (no microbial confirmation, with a clinical course compatible with hospital-acquired pneumonia and ventilator-associated pneumonia).

Bacteremia: The presence of viable bacteria in the circulating blood detected by hemoculture.

Surgical site infection: (i) Superficial: Within 30 days after surgery AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: a) purulent drainage from the superficial incision, b) organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiological method, c) superficial incision deliberately opened by a surgeon/physician and testing is not performed AND patient has at least one of the following: pain or tenderness, localized swelling, erythema, or heat, d) diagnosis of a superficial incisional surgical site infection. (ii) Deep: Within 30 or 90 days after surgery AND involves deep soft tissues of the incision, AND patient has at least one of the following a) purulent drainage from the deep incision, b) deep incision that spontaneously dehisces or is deliberately opened or aspirated by surgeon/physician and organism identified by microbiological method AND patient has at least one of the following: fever

(>38 °C), localized pain or tenderness, c) an abscess or other evidence of infection involving deep incision detected on gross anatomical or histopathologic exam.

Convulsion/seizure: A seizure is a brief episode that can range from uncontrolled jerking movements (convulsive seizure) to a subtle momentary loss of awareness (absence seizure). Seizures can occur in people who do not have epilepsy for reasons such as brain trauma, drug use, elevated body temperature (febrile seizure), or hypoglycemia.

Meningitis or Ventriculitis: At least one of the following criteria: 1) organism(s) identified from CSF by microbiological method, 2) patient has at least 2 of the following: fever (>38.0 °C) or headache, meningeal signs, cranial nerve signs, AND at least one of the following: a) increased white cells, elevated protein, and decreased glucose in CSF, b) organism(s) seen on Gram stain of CSF, c) organism(s) identified from blood by microbiological method, d) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Brain abcess: At least one of the following criteria: 1) organism(s) identified from brain tissue by microbiological testing method, 2) patient has an abscess or evidence of intracranial infection on gross anatomic or histopathologic exam, 3) patient has at least 2 of the following: headache, dizziness, fever (>38.0 °C), focal neurological signs, altered level of consciousness, or confusion, AND at least one of the following: a) organisms detected on microscopic examination of brain tissue, b) evidence suggestive of infection on imaging test (if equivocal supported by clinical correlation), c) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic shock: A subclass of sepsis where circulatory and cellular/metabolic abnormalities are severe enough (persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg, and with a serum lactate level >2 mmol/L despite volume resuscitation) to substantially increase mortality.

Deep vein thrombosis (proximal DVT): Partially or completely incompressible venous segment of the proximal venous system, assessed at six sites (common femoral, proximal, middle, and distal superficial femoral, and popliteal veins and the venous trifurcation) by Doppler ultrasound. Wall thickening is not diagnostic of DVT.

Pulmonary embolism (PE): Definite (intraluminal filling defect on chest CT scan, a high-probability ventilation-perfusion scan, or autopsy finding), probable (high clinical suspicion and either no test results or nondiagnostic results on noninvasive testing), possible (clinical suspicion and nondiagnostic results on noninvasive testing).

Major bleeding: Defined as hemorrhage occurring at a critical site (i.e., intracranial, pericardial, or retroperitoneal), resulting in hypovolemic shock (i.e., ruptured abdominal aortic aneurysm, upper or lower GI bleed), resulting in the need for a major therapeutic intervention (i.e., surgery), requiring at least 2 units of RBC concentrates, or resulting in death.

Stroke: Poor blood flow to the brain resulting in cell death. There are two principle types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding (or intracranial hemorrhage (ICH)).

Transfusion reactions: The most common complications of transfusions are febrile non-hemolytic reactions, and allergic reactions with urticaria. The most serious complications include an anaphylactic reaction, transfusion-associated cardiac overload (TACO), transfusion-related acute lung injury (TRALI), and acute hemolytic reaction due to ABO incompatibility. Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.

Febrile non-hemolytic reactions:
Fever (> 1 °C with respect to base temperature) with or without shivering at the end of the transfusion or shortly afterwards, that can be accompanied by tachycardia.
- No drop in blood pressure, no lumbar pain, no urticaria, no bronchospasm

Allergic reactions with urticaria:
Urticaria and pruritis at the end of the transfusion, rarely with cough or slight difficulty breathing.
- No drop in blood pressure, no chest tightness, no angioedema

Anaphylactic reaction:
Can happen soon after the start of transfusion. Urticaria, general malaise, chest tightness, edema of the face and glottis, difficulty breathing, drop in blood pressure, bronchospasm.
- Not necessarily with fever initially.

Transfusion-Associated Cardiac Overload (TACO):
Dyspnea during or after the transfusion with tachycardia, crackling sounds at base of lungs ± S3 galop. Sometimes with bronchospasm. Edema/overload on chest X-ray.
- No fever, no drop in pressure, no urticaria.

Transfusion-related acute lung injury (TRALI):
Dyspnea 2–6 h post-transfusion with progressive severe respiratory distress requiring O2 and mechanical ventilation. Diffuse bilateral infiltrations on chest X-ray. Can present with fever and hypotension.

- No urticaria or angioedema. Difficult to distinguish from acute cardiogenic pulmonary edema.

Acute hemolytic reaction due to ABO incompatibility:
Typically 10–20 min after the start of transfusion. Sudden severe malaise with chest tightness, lumbar pain, fever, dyspnea, tachycardia and drop in pressure.
- No urticaria, no angioedema, no bronchospasm, no crackling in lungs on auscultation.

Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.
Note that expected events include transfusion reactions and therefore a transfusion reaction should not be reported as an SAE.

Appendix 3: Data Safety Monitoring Committee Charter

HEMOTION Data Safety and Monitoring Committee Charter

ClinicalTrials.gov Identifier : NCT03260478

Coordinating centre : **CHU de Québec — Université Laval**

Data Management : **Ottawa Hospital Research Center (OHRI)**

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TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

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TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

List of Abbreviations

CHU:	Centre Hospitalier Universitaire
CRF:	Case Report Form
DSMC:	Data Safety Monitoring Committee
PC:	Project Coordinator
PI:	Principal Investigator
REB:	Research Ethics Board
SC:	Steering Committee
TBI:	Traumatic Brain Injury

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

1. HEMOTION trial Organization in Relation to DSMC

The HEMOTION trial DSMC charter is based in part on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter[1]. This charter outlines the roles, responsibilities, timing, frequency and format of meetings, methods of providing information to and from the DSMC, statistical issues, and relationships of the DSMC to the Principal Investigators (PIs) [Alexis F Turgeon, Dean Fergusson and François Lauzier], Project Coordinator (PC), Steering Committee (SC) [see Appendix 1], Trial Statistician, Investigators, Trial Participants, Institutional Research Ethics Boards (REBs), Sponsor [CHU de Québec-Université Laval and Université Laval], Funding Agency [Canadian Institutes of Health Research] and the Canadian Critical Care Trials Group.

2. DSMC Members

The HEMOTION trial DSMC members include: Dr. Darrell Triulzi (University of Pittsburgh), an international expert in transfusion medicine; Dr. Jonathan Cook (University of Oxford), a senior biostatistician and epidemiologist involved in several clinical trials; and Dr. Claude Hemphill (University of California, San Francisco), a neurologist and expert in neurocritical care. The DSMC members are not part of the HEMOTION trial team and were not involved in the development of this proposal.

3. Overview of DSMC Responsibilities

The ongoing primary responsibilities of the DSMC will involve the independent review of reports received directly from the Methods Centre regarding:

1. Recruitment (centre and patient), consent rates and co-enrolment rates
2. Protocol procedures (randomization, protocol violations)
3. Canadian Institutes of Health Research reports
4. Sample data management tables (data completeness, accuracy, timeliness)
5. One interim and final analyses (baseline characteristics, primary, secondary and tertiary outcomes, and serious adverse events)
6. Study metrics at 25, 50 and 75% of enrolment
7. Abstract review

The DSMC will monitor performance and provide suggestions and recommendations as required to protect the validity and credibility of the trial. The DSMC will receive and evaluate all serious adverse events at the time of the interim analyses to safeguard the interest of study participants.

4. Overview of Sample Size Calculation

Our sample size is based on the proportion of moderate and severe TBI patients with an unfavourable outcome (GOSe$\leq$ 4)[2-4]. Assuming a 40% risk of an unfavourable outcome in the restrictive group[3,4], 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 1 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. Our sample size will also allow to detect a 10-point difference on the FIM score with 99% power (assuming a baseline score of 95 and a standard deviation of 10).

5. Overview of Warning Guides

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 $\leq$ 4), and using the sliding dichotomy approach to account for the whole ordinal scale[5]. 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 and used in recent NINDS-funded trials to increase the ability to detect smaller effect size with similar power. We will assess the baseline prognosis risk with the externally validated CRASH prognostic model[6]. Subjects will be split into 6 quantiles 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 $\geq$3. Patients categorized in the best prognosis quantile will be considered to have a favourable outcome if the 6-month GOSe is $\geq$8. 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 (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.

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

The DSMC may or may not consider a significant difference for harm between groups at this interim analysis to be sufficient grounds to recommend suspending enrolment. Other considerations may influence recommendations such as other outcome results, methodological or practical concerns, or external evidence. The DSMC will inform the PIs and SC if, in their view, major safety issues have arisen that are likely to convince a

broad range of clinicians, including those supporting the trial and the general clinical community, that on balance, some aspect of the trial is potentially harmful for all or a particular subgroup of patients.

After the interim analysis, the DSMC will:

1. recommend whether to continue patient enrolment;
2. recommend whether to suspend enrolment until careful review by the PIs and SC;
3. recommend whether more information is required before a recommendation can be made;
4. recommend whether to terminate enrolment.

6. Specific Responsibilities of the DSMC

1. To aid the PIs and SC by providing advice about the conduct of the trial and integrity of the data, so as to protect the validity of the trial, current and future patients.
2. To ensure the overall safety of trial patients by protecting them from avoidable harm.
3. To also review study metrics at 25, 50 and 75% enrolment.

7. Relationship with the Principal Investigators and Steering Committee

1. The DSMC is independent of the PIs and SC in operating and formulating recommendations, but is supportive of the aims and methods of the trial.
2. The DSMC serves in an advisory role to the PIs and SC.
3. The PIs and SC receive DSMC recommendations under advisement.
4. The DSMC, PIs and SC work collaboratively to ensure rigorous, safe and timely conduct of the trial.

8. Initial Responsibilities of the DSMC

1. Review the DSMC Charter and the protocol.
2. Review, discuss, debate and approve the Methods Centre operations.
3. Review, discuss, debate and approve the mechanisms for transmitting serious adverse event information to the DSMC.
4. Establish guidelines for calling emergency meetings of the DSMC.
5. Propose a schedule for subsequent DSMC meetings, acknowledging that the Chair may call for a meeting of the DSMC at any time, as may the PIs.
6. Approve or refine template tables provided by the PIs and Trial Statistician for future review at the interim analyses.

7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the intervention, investment, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other dual loyalties, etc. Decisions concerning whether an individual with a real or perceived conflict of interest may participate on the DSMC will be made by the DSMC Chair.

9. Ongoing Responsibilities of the DSMC

The DSMC is responsible for helping to ensure that patients in the HEMOTION trial are not exposed to unnecessary or unreasonable risks and that the trial is conducted according to the highest scientific and ethical standards. The DSMC will:

1. Review data from the planned interim analysis provided by the PI and SC.
2. Alert the PIs and SC about scientific, procedural or ethical concerns emerging from the interim analysis and from the final trial results.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data (provided by the PIs and SC) that may impact on patient safety or the efficacy of the study intervention.
5. Provide recommendations for adjustment of the sample size or trial termination.
6. Read and provide suggestions for manuscript publications before submission.
7. Be acknowledged in the main report, unless requested otherwise.

10. Timing of Meetings

The DSMC will meet:

1. Once initially to discuss the protocol and analysis plans, the DSMC Charter, template tables, and to clarify any aspects with the PIs and SC.
2. At the time of the interim analysis.
3. At the end of the trial to allow the DSMC to discuss the final data with the PIs and SC to advise on data interpretation.
4. As needed, in person or by teleconference.

11. Responsibilities of the Principal Investigators and Project Coordinator

1. The PIs and PC will provide the DSMC Charter, protocol and CRFs to the DSMC before the initial meeting.
2. The PIs and PC will provide preliminary template reports of recruitment (centre and patient) and consent rates; procedures (randomization errors, crossovers, protocol adherence, protocol violations); data management (data completeness, accuracy, timeliness and query resolution); physiologic safety data; funding agency reports; one interim and final analyses (baseline characteristics, primary, secondary and tertiary outcomes, and serious adverse events) and abstracts to date.

3. The PIs and SC will modify these template reports as requested to create tables for the interim analysis.
4. For baseline characteristics and outcomes, the Trial Statistician blinded to the group allocation will provide to the DSMC, data according to group A and B, including baseline characteristics (age, sex, TBI severity, etc.), primary, secondary and tertiary outcomes and serious adverse events.
5. The PIs, SC and Trial Biostatistician will ensure that DSMC members remain blinded to allocation.
6. The PIs and SC will provide the results of any new relevant external published data for DSMC consideration.

12. Three-Part Structure of DSMC Meetings

1. First, an open session will be held with the PIs, PC and Trial Statistician. The purpose will be to review accrual, data timeliness and quality, completeness of the follow-up and adjudication, serious adverse events, problems with specific centres, and any proposals for changes in the trial protocol or duration. In addition, the PIs will report any new external evidence (especially results from other relevant ongoing studies) that bear on the conduct of the trial.
2. Second, a partially closed session between the DSMC and the Trial Statistician to review the primary, secondary and tertiary outcomes separated by group and presented in a blinded fashion (group A and group B). These data will not be available to the PI, PC, SC, or Investigators except as authorized by the DSMC Chair. The PIs will receive data in aggregate form.
3. Third, a totally closed session for just the DSMC members to discuss the emerging results, decide on recommendations, and draft comments and recommendations.

13. Potential Unblinding of the DSMC

1. During the closed session, if the DSMC deems it crucial to their interpretation of the data, the DSMC will request unblinding themselves to group assignment without informing the investigative team of this need.
2. The request to unblind would need to be based on findings that are extreme and unambiguous, and the decision of the DSMC to request unblinding should be unanimous.
3. To achieve unblinding, the DSMC will have immediate access to the Data Management personnel at the OHRI Methods Center. An independent statistician will redo analyses if requested. The PI, SC and Trial Statistician will not review the unblinded results.

14. Discussions of the DSMC

1. Efforts should be made for the DSMC to reach unanimous recommendations.
2. The role of the Chair is to summarize discussions and encourage consensus.

3. Before making any recommendations, the DSMC should consider the ethical, scientific, statistical, practical and financial implications for the trial.

15. Minutes of DSCM Meetings

1. Within a week of each DSMC meeting, the Chair will generate minutes of the open and closed sessions of the meeting.
2. The minutes will contain the major points of discussion, recommendations made, and any additional information requested for future meetings.
3. Minutes of the open session of the meeting will be for the PIs, PC and SC.
4. Minutes of the closed session will be for the DSMC members only, until the trial is complete.

16. Reports of the DSMC

1. After each DSMC meeting, the Chair will report to the PIs and SC. Each meeting will be summarized in two reports (one short report suitable for Investigators, the sponsor, REBs and the funding agency) and one more detailed report for the PIs, PC and SC.
2. If accepted by the SC, the PIs will circulate the DSMC's short and long reports to the appropriate personnel.
3. If the DSMC recommends continuing enrolment in the trial following an interim analysis, no other information shall be provided to the PI and SC.
4. If the DSMC recommends suspending enrolment of the trial until a careful review by the PI and SC; or whether more information is required before a recommendation can be made, or whether to terminate enrolment, the DSMC will provide a full report of the rationale to the PIs, PC and SC.

17. Conflict Resolution

1. In the event that the PIs or the SC disagree with the DSMC recommendations to modify or to terminate the trial, a third party arbitrator may be called upon.
2. A third party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (ideally both methodological and clinical), to make a final decision.
3. The selection of the third party arbitrator will be made by mutual consent of both the PIs and the DSMC Chair.
4. It is the responsibility of the PIs to notify the Investigators, the sponsors and participating REBs of any recommendations about trial modification or enrolment suspension or termination.

18. Confidentiality

1. It is the duty of each member of the DSMC to protect the confidentiality of the trial and the results of monitoring.
2. The members of the DSMC acknowledge that the data emerging from this trial are the collective property of the PI, SC and Investigators.
3. DSMC members will not have the right to present or publish data from this trial anywhere without the explicit permission of the PIs and SC, and not until after the trial is complete.
4. DSMC members will not act as representatives for the study, nor address questions that may arise about the trial.

19. Reporting on the DSMC

1. A brief summary of the roles, responsibilities, and recommendations of the DSMC will be included in the trial manuscript.
2. DSMC members will be invited to read and comment on the trial manuscript, including any statement related to the DSMC.
3. DSMC members will be named and their affiliations listed in the trial manuscript, unless requested otherwise.

20. References

1. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet.* 2005 ; 365(9460) : 711-722.
2. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1974 ; 2(7872) : 81-84.
3. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. *Lancet.* 2015 ; 386(10012) : 2499-2506.
4. Wright DW, Yeatts SD, Silbergleit R, et al. Very Early Administration of Progesterone for Acute Traumatic Brain Injury. *N Engl J Med.* 2014:141210140028006.
5. Murray GD, Barer D, Choi S, et al. Design and analysis of phase III trials with ordered outcome scales: the concept of the sliding dichotomy. *J Neurotrauma.* 2005;22(5):511-517.
6. MRC CRASH Trial Collaborators, Perel P, Arango M, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ.* 2008;336(7641):425-429.

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

APPENDIX 1. Members of the Steering Committee

Investigators

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

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

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

Algird, Almunder. McMaster University, Hamilton (Ontario), Canada

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

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

Charbonney, Emmanuel. Université de Montréal, Montréal (Québec), Canada

Chassé, Michaël. Université de Montréal, Montréal (Québec), Canada

Docherty, Annemarie. The University of Edinburgh, Edinburgh, United Kingdom

Dubé, Jean-Nicolas. Centre intégré universitaire de santé et de services sociaux de la Mauricie-et-du-Centre-du-Québec, Trois-Rivières (Québec), Canada

English, Shane. Ottawa Health Research Institute, Ottawa (Ontario), Canada

Green, Rob. Dalhousie University, Halifax (Nova Scotia), Canada

Griesdale, Donald. University of British Columbia, Vancouver (British Columbia), Canada

Hébert, Paul. Université de Montréal, Montréal (Québec), Canada

Khwaja, Kosar. McGill University Health Center, Montréal (Québec), Canada

Kramer, Andreas. University of Calgary, Calgary (Alberta), Canada

Kutsogiannis, Jim. University of Alberta, Edmonton (Alberta), Canada

Lamontagne, François. Université de Sherbrooke, Sherbrooke (Québec), Canada

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

Laroche, Vincent. CHU de Québec-Université Laval, Québec (Québec), Canada

Lessard-Bonaventure, Paule. CHU de Québec-Université Laval, Québec (Québec), Canada

Malbouisson, Luiz. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

Marshall, John. St. Michael's Hospital, Toronto (Ontario), Canada

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

Pili-Flouri, Sébastien. Centre Hospitalier Universitaire de Besançon, Besançon, France

Rigamonti, Andrea. St. Michael's Hospital, Toronto (Ontario), Canada

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

St-Onge, Maude. CHU de Québec-Université Laval, Québec (Québec), Canada

Tinmouth, Alan. Ottawa Hospital Research Institute, Ottawa (Ontario), Canada

Verret, Michaël, CHU de Québec-Université Laval, Québec (Québec), Canada

Walsh, Tim. The University of Edinburgh, Edinburgh, United Kingdom

Zarychanski, Ryan. University of Manitoba, Winnipeg (Manitoba), Canada

Knowledge users

Brain Injury Association of Canada

Canadian Anesthesiologists Society

Canadian Critical Care Trials Group

Canadian Critical Care Society

Institut national d'excellence en santé et services sociaux

Héma-Québec

Appendix 4 : Informed Consent Form

Information Sheet and Consent Form

Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Principal Investigators:

Dr Alexis Turgeon
Department of Critical Care Medicine
CHU de Québec — Université Laval

Dr François Lauzier
Department of Critical Care Medicine
CHU de Québec — Université Laval

Dr Dean Fergusson
Clinical Epidemiology Program
Ottawa Hospital Research Institute

Local Investigator LOCAL INVESTIGATOR NAME(S)

Local Co-Investigators: LOCAL CO-INVESTIGATOR NAME(S)

Granting Agency: Canadian Institutes of Health Research

Preamble

We request the participation of the person you represent in a research project. However, before accepting and signing this information sheet and consent form, please take the time to read, understand and carefully consider the following information.

This document may contain words that you do not understand. We invite you to ask any questions you may find useful to the Investigator in charge of this project or to the research staff. You may also ask them to explain any word or information that is not clear.

Objectives of this Research Project

The person you represent is currently hospitalized in the intensive care unit (ICU) following a traumatic brain injury (TBI). TBI is an important cause of disability and can result in severe sequelae. TBI victims often have low hemoglobin levels (anemia) for a variety of reasons. This low level of hemoglobin can lead to additional sequelae by decreasing oxygen delivery to the brain. Generally, doctors prescribe transfusions of red blood cells (blood transfusion) when the hemoglobin is below 70 g/L to maintain oxygen delivery. However, we ignore if it would not be better to aim for higher hemoglobin levels.

The main objective of this study is to evaluate whether maintaining hemoglobin levels above 100 g/L (rather than 70 g/L) with red blood cell transfusions reduces the sequelae caused by the TBI.

This study will take place in several sites across Canada and the UK and will involve approximately 712 patients. The study will last approximately 4 years.

Procedures of the Research Project

If the hemoglobin level of the person you represent is below 100 g/L, the participant will be randomly assigned (such as flipping a coin) to one of two groups:

A computer will randomly determine in which group the person you represent will be assigned. There will be a 50% chance (1 chance out of 2) to be assigned to one of the following groups:

Group 1: Transfusion of red blood cells if the hemoglobin level is less than or equal to 100 g/L
Group 2: Transfusion of red blood cells if the hemoglobin level is less than or equal to 70 g/L

The study intervention will last until you are discharged from the ICU.

The assignment group will not be communicated to you or to the person you represent.

The medical team may have decided to proceed with a blood transfusion as part of this Research Project before obtaining your consent given the urgent need to maintain proper oxygen transport to the brain. If you refuse to allow the person you represent to continue participating, the decision to transfuse will be left to the ICU team. At any time, the physician of the person you represent may terminate study participation if he/she believes it is in the best interests of the participant.

If the person you represent participates in this study, we will collect information from her/his medical record. Her/his contact information will be provided to the coordinating research team. Six months later, a member of the coordinating research team will get in touch with the person you represent to obtain information on the consequences of the TBI, the level of activity, the mental health and the quality of life. This information will allow to evaluate the effect of the study intervention. This should take about 30 to 45 minutes and will be done by phone call or with electronic questionnaires to be completed online (when possible). It is possible that the person you represent will not be able to answer some of the questions due to her/his condition. In this case, we will ask a representative of the patient (yourself or someone else) to answer the questions on behalf of the patient.

Benefits Associated with the Research Project

The person you represent may benefit from participating in this Research Project, but we cannot guarantee this. However, the results of the Research Project will contribute to the advancement of scientific knowledge and may benefit future patients.

Risks Associated with the Research Project

Most patients with TBI will receive red blood cell transfusions during their hospitalization. In this study, patients allocated to Group 1 may receive more transfusions than patients allocated to Group 2.

The risks incurred by study participants are the same as those incurred by non-study patients receiving transfusions.

The side effects of red blood cell transfusions include:

- Uncommon (fewer than 1%)
  - Fever
  - Skin rash
- Rare (fewer than 0.1%)
  - Serious allergic reaction that may be life-threatening
  - Transfusion reactions associated with red blood cell damage
  - Lung injury
  - Fluid overload in the lungs
- Very rare (fewer than 0.001%)
  - HIV, Hepatitis B, Hepatitis C. The Canadian system of blood collection and distribution is safer than ever, but it will never be possible to ensure that blood transfusion is free of any risk of disease transmission or infection.

Disadvantages of the questionnaires:

It is possible that some questions may make you or the person you represent feel uncomfortable. The questionnaires do not generate any other disadvantage, except the time devoted to them.

Voluntary Participation and Possibility of Withdrawal

Participation in this Research Project is voluntary. You, and the person you represent, are free to refuse to participate. You, and the person you represent, can also withdraw at any time by informing the research team, without providing an explanation.

The decision not to participate or withdraw from this Research Project will have no impact on the quality of the care and services provided to the person you represent. It will not have an impact on your relationship with healthcare providers.

The Investigators, the Research Ethics Committee of the *CHU de Québec - Université Laval* and the Canadian Institutes of Health Research may terminate the participation of the person you represent to this Research Project without consent if new discoveries or data indicates that it is no longer in the best interest of the participant, if the participant is unable to comply with instructions or if there are administrative reasons for abandoning the Project.

However, before the person you represent withdraws from this Research Project, we suggest to, for security purposes, make a final evaluation by phone.

In case of withdrawal, the data and material already collected will nevertheless be retained, analyzed and

used if necessary to comply with regulatory requirements and ensure the integrity of the project.

Any new knowledge that may affect your decision or the decision of the person you represent to participate will be immediately communicated to you.

Confidentiality

During this project, the Investigators and their staff members will collect and record information of the person you represent in a research folder. Only information necessary to meet the scientific objectives of the project will be collected.

This information may include information contained in medical records regarding past and present health status, lifestyle, and investigation results, physical examinations and procedures that will be performed during this Research Project. This data will be retained by the Investigators for 10 years.

All information collected is strictly confidential to the extent permitted by the law. The person you represent will only be identified by a code number. The key of the code linking the participant's name to the research folder will be kept by the Investigators.

To ensure the safety of the person you represent, a copy of this Information Sheet and Consent Form will be included in the medical record. Therefore, anyone who has access to the medical record will have access to the information that the document contains.

The local investigator will forward the coded research data on the person you represent to the Principal Investigators or their representatives (coordinating team). Increasingly, the scientific community, the granting agencies and medical scientific journals require that data be stored and made available for secondary review and analyses. For publication purposes the de-identified study data may be shared for re-analyses. Your family member's coded research data may also be transmitted by the principal investigator to other researchers from other institutions for secondary analyses or other research purposes. It will not be possible to identify any individual including yourself in any publication.

For surveillance, control, protection and safety purposes, the research folder and the medical records of the person you represent may be consulted by Canadian (e.g. such as Health Canada) or foreign regulatory bodies, by representatives of the Canadian Institutes of Health Research, by institutional representatives or by the Research Committee. These individuals and organizations all adhere to a privacy policy.

You have the right to consult the research folder of the person you represent to verify the information collected and have it corrected if necessary. However, to preserve the scientific integrity of the project, you may only be able to access some of this information once their participation in the Research Project is completed.

Compensation

There is no financial compensation for participating in this Research Project.

Indemnity in Case of Injury and Participant's Rights

If the person you represent should suffer any prejudice because of any procedure related to this Research Project, all the necessary care and services required will be provided.

By agreeing to participate in this Research Project, you do not waive any right or release the Investigators,

the institution and the Canadian Institutes of Health Research from their civil and professional liability.

Contacts

If you have questions about the Research Project or if the person you represent has problems that you believe are related to their participation in the project, you can contact the Local Investigator (TELEPHONE NUMBER), the research team (TELEPHONE NUMBER) or go to the nearest Emergency Room.

If you have any questions about the rights of the person you represent, or if you have any complaints or comments, you can contact the Local Service Quality and Complaints Commissioner of the *CHU de Québec — Université Laval* at 418-654-2211.

Monitoring ethical aspects of the research project

The Research Ethics Board of the CHU de Québec-Université Laval approved this research project and ensures the follow-up for all participating institutions of the health and social services network of the province of Québec.

Consent Form
(Temporarily Incapacitated Adult Participant)

Title of the Research Project: Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Since Mr./Mrs. _____ has been suddenly rendered incapable to consent for the reason identified below, the *Code civil du Québec* authorizes you, as _____ (your relationship with the participant) to consent for the person you represent to participate in this research project.

As soon as Mr. / Mrs. _____ is recovered, we will invite her/him to sign the consent form so that he/she can indicate his/her desire to continue or not to participate in the Research Project.

Reason why the participant cannot consent:

_____

I have read the Information Sheet and Consent Form. The research project and this Information Sheet and Consent Form was explained to me. My questions were answered and I was given the time to decide to participate. After consideration, I consent that the person I represent participates in this Research Project under the conditions defined therein. I also authorize the research team to have access to the medical records of the person I represent.

I authorize the family doctor of the person I represent to be informed of the study participation.

☐ Yes ☐ No

_____
Name of the participant (please print)

_____
Name of the person qualified to give consent for care (relationship with the participant) (please print)

_____ _____
Signature of the person qualified to give consent for care Date

Signature of the person who obtained consent if different from the Local Investigator

I explained the Research Project and the Information Sheet and Consent Form to the person qualified to give consent for care, and I answered the questions he/she asked me.

_____

Name of the person who obtained consent (please print)

_____ _____

Signature of the person who obtained consent Date

Consent Form
(Temporarily Incapacitated Adult Participant who Regained Capacity)

Title of the Research Project: Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Your legal representative gave consent for your participation in this study because you were not able to decide due to your health condition. Your condition has now improved. We therefore ask you to decide whether you wish to continue your participation in this study. Your decision is voluntary. This means that the decision belongs to you.

You have read the information provided in this information and consent form and someone has explained to you which procedures of the study will be continued. Your questions were answered at your satisfaction. You believe you have understood all the information related to this study.

Participant Consent

I am now able to make my own decisions and:

_____ (initials) I agree to continue my participation in this study.

_____ (initials) I do not agree to continue my participation in this study. I understand that the data already collected may nevertheless be used for this study to ensure its reliability.

_____
Name of the Participant (please print)

_____ _____
Signature of the Participant Date

Signature of the person who obtained consent if different from the Local Investigator

I certify that the Research Project and this Information Sheet and Consent Form have been explained to the participant. I have answered all the questions and I have made it clear that the participant remains free to terminate his participation, without prejudice.

_____

Name of the person who obtained consent (please print)

_____ _____

Signature of the person who obtained consent Date

Appendix 5 : Protocol Revision History

Version Number	Summary of Revisions Made	Version Date
1.0	n/a	July 11, 2017
2.0	• Addition of the Clinical trials.gov registration number • Correction of typos and wording • Update of the list of abbreviations • Precision regarding one exclusion criteria (fixed bilateral dilated pupils) • Modification to the size of permuted blocks for randomization (4 and 6 instead of 2 and 4) • Update of the list of participating sites and anticipated recruitment rate • Modification of the interim analysis (one analysis at 50% enrolment instead of 2 analyses at one third and two thirds) • Modification of the time frame to report protocol violations at the Coordinating Centre (72 hours instead of 96 hours)	Nov 22, 2017
3.0	• Increase in sample size • Addition of Withdrawal of Life-Sustaining Therapies as a trigger to stop applying the intervention • Addition of the PACT as a collaborative research network • Minor corrections to the text and references • Clarification of secondary and tertiary objectives • Addition of patient minimum age • Clarification of potential protocol violation definitions and management • Precision regarding the start and end of treatment strategy • Modification of the list of participating centres • Increase in recruitment period • Precision on required imaging results • Deletion of one secondary outcome (return to work) • One secondary outcome changed to tertiary outcome (complications related to transfusion) • Modification of the statistical and analytic plan for the primary outcome, of subgroup and sensitivity analyses • Modification to how follow-ups are organized • Update of References • Update of Steering Committee members and Knowledge users	May 17, 2022

Section/item	Item No	Description	Addressed on page number
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Introduction

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Methods: Participants, interventions, and outcomes

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Methods: Assignment of interventions (for controlled trials)&

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Methods: Data collection, management, and analysis&

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Methods: Monitoring&

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Ethics and dissemination

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Hemoglobin transfusion threshold in traumatic brain injury optimization (HEMOTION): a multicenter, randomized, clinical trial protocol

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Article Type:	Protocol
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Hemoglobin transfusion threshold in traumatic brain injury optimization (HEMOTION): a multicenter, randomized, clinical trial protocol

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is the leading cause of mortality and long-term disability in young adults. Despite the high prevalence of anemia and red blood cell (RBC) transfusion in TBI patients, the optimal hemoglobin (Hb) transfusion threshold is unknown. We undertook a randomized trial to evaluate whether a liberal transfusion strategy improves clinical outcomes compared to a restrictive strategy.

Methods and analysis: HEMOTION is an international pragmatic randomized open label blinded-endpoint clinical trial. We will include 742 adult patients admitted to an intensive care unit (ICU) with an acute moderate or severe blunt TBI (Glasgow Coma Scale [GCS] ≤ 12) and a Hb level ≤100 g/L. Patients are randomly allocated using a 1:1 ratio, stratified by site, to a liberal (triggered by Hb ≤100 g/L) or a restrictive (triggered by Hb ≤70 g/L) transfusion strategy applied from the time of randomization to the decision to withdraw life-sustaining therapies, ICU discharge, or death. Primary and secondary outcomes are assessed centrally by trained research personnel blinded to the intervention. The primary outcome is the Glasgow Outcome Scale extended (GOSe) at 6 months. Secondary outcomes include overall functional independence measure (FIM), overall quality of life (EQ-5D-5L), TBI specific quality of life (QOLIBRI), depression (PHQ-9) and mortality.

Ethics and dissemination: This trial is approved by the CHU de Québec—Université Laval research ethics board (MP-20-2018-3706) and ethic boards at all participating sites. Our results will be published and shared with relevant organizations and healthcare professionals.

Trial registration number: ClinicalTrials.gov Identifier: NCT03260478.

STRENGTHS AND LIMITATIONS OF THIS TRIAL

- The multicenter international recruitment and our pragmatic approach will provide generalizable findings.
- The blinded outcome assessment will minimize ascertainment bias.
- The sample size and sliding dichotomy analysis will increase our ability to detect smaller effect size with similar power for a given population size.
- Transfusions administered as part of the initial resuscitation of acute trauma prior to ICU admission will not be protocolized.

INTRODUCTION

Traumatic brain injury (TBI) is a significant public health concern and represents the leading cause of mortality and long-term disability in young adults[1]. For these patients, the cerebral autoregulation that normally compensates for variations in oxygen delivery is impaired[2], rendering their brain vulnerable to ischemia and secondary injuries. In the absence of high-quality evidence, several experts have suggested maintaining higher hemoglobin (Hb) levels (>100 g/L) on the assumption that it reduces metabolic distress and improves brain tissue oxygenation[3-5]. The adoption of a liberal transfusion strategy has important resource implications since most patients with TBI will develop anemia[6] and approximately one third will be transfused during their hospital stay[7].

The evidence to support transfusion strategies in patients with TBI remains scarce. In a systematic review of studies in neurocritical care patients, we found insufficient evidence to support the use of a specific transfusion threshold to improve morbidity and mortality[8]. A recent randomized controlled trial showed no effect of RBC transfusion on neurological outcomes in patients with moderate or severe TBI, although the expected effect size was large and most patients included were not anemic[9]. To date, clinical practice guidelines are based on limited evidence and do not provide clear recommendations regarding RBC transfusion in TBI[10 11]. As a result, transfusion practices vary greatly within and between centres[12 13]; many clinicians extrapolate the evidence supporting the non-inferiority of a restrictive strategy in critically ill patients without TBI[14 15] while others advocate for a liberal transfusion strategy pending stronger evidence to support this practice[16].

In collaboration with the Canadian Critical Care Trials Group (CCCTG), the Perioperative Anesthesia Clinical Trials group (PACT) and the Canadian Traumatic Brain Injury Research

Consortium (CTRC), we designed the HEMOTION (**HEMO**globin **T**ransfusion Threshold in Traumatic Brain **I**njury Optimizati**ON**) trial. The primary objective of our international pragmatic randomized open label blinded-endpoint (PROBE)[17] trial is to evaluate whether a liberal (higher Hb threshold) vs. a restrictive (lower Hb threshold) RBC transfusion strategy improves neurological outcomes in anemic moderate and severe TBI patients admitted to the intensive care unit (ICU). Secondary objectives will evaluate the effect of transfusion strategies on functional outcome, quality of life, depression, and mortality. Tertiary objectives will evaluate the effect of transfusion strategies on the incidence of transfusion-related complications, infections, Hb levels, number of RBC units transfused, and ICU and hospital length of stay. Herein, we report the trial protocol according to the SPIRIT statement[18]. This trial is registered with ClinicalTrials.gov (Identifier: NCT03260478).

METHODS AND ANALYSIS

Trial Settings and Eligibility Criteria

The HEMOTION trial is being conducted in level 1 and level II trauma centres in Canada, the United Kingdom, Brazil and France since September 2017. We are recruiting adult patients (≥18 years-old) admitted to the ICU with an acute (hospital admission within 24 hours of injury) moderate or severe (Glasgow Coma Score [GCS] ≤12)[19] blunt TBI and a Hb level ≤100 g/L. We exclude patients who receive transfusion after ICU admission, have contraindications or known objection to transfusions, or have no fixed address. We also exclude patients who meet the criteria for neurological determination of death, those with a GCS of 3 in combination with bilateral fixed dilated pupils, those with active life-threatening bleeding associated with hemorrhagic shock, and patients for whom a decision to withhold or withdraw life-sustaining therapies has been made at

the time of screening. Patients who received transfusion prior to ICU admission (e.g., in the emergency room or in the operating room), as part of the initial acute trauma resuscitation, are eligible. Research coordinators at each participating site screens daily all critically ill adult patients with TBI to determine eligibility. Table 1 depicts the schedule of interventions, data collection and outcome assessments. In the final report, we will report excluded patients and reasons for non-enrollment using the CONSORT flow diagram[20] (Figure 1).

Assignment of Interventions

Upon reaching a Hb ≤ 100 g/L and after a site investigator confirms eligibility, the research coordinator uses a secure, web-based, central, concealed, computerized randomization portal to allocate patients in a 1:1 ratio to either a liberal (experimental) or a restrictive (control) RBC transfusion strategy. Randomization is done with variable permuted blocks of 4 and 6, stratified by site. Staff members of the methods centre of the Ottawa Health Research Institute (OHRI) who are not involved in trial implementation generated the randomization sequence.

Interventions

Once randomized, the trial intervention is initiated within three hours in patients meeting the threshold for transfusion in their respective group to avoid prolonged exposure to Hb levels below this threshold.

Experimental Intervention: Liberal Transfusion Strategy

Patients in the liberal transfusion strategy group receive an RBC transfusion if their Hb is ≤100 g/L. This threshold, shown to be effective in maintaining adequate cerebral oxygenation[3-5],

is considered acceptable by clinicians caring for critical care patients with neurological injuries[16 21].

Control Intervention: Restrictive Transfusion Strategy

Patients in the restrictive transfusion strategy group receive an RBC transfusion only if their Hb is ≤70 g/L. We have chosen this threshold because it is the most studied restrictive RBC transfusion threshold[14 15] and reflects the current standard of care in non-bleeding critically ill patients without neurological or coronary artery diseases[11]. It also is a frequently used and accepted threshold for clinicians who care for brain-injured patients[16].

Duration of Treatment

The allocated transfusion strategy is applied throughout the ICU stay until ICU discharge, death, or a decision to withdraw life-sustaining therapy is made, whichever comes first. The study procedures are also implemented in the operating room, provided the patient is still admitted to the ICU. A single unit at a time is transfused when the Hb threshold is reached unless there is an active and uncontrolled bleeding requiring urgent care. Additional RBC transfusions are given if the post-transfusion Hb level remains below the assigned threshold. In both groups, RBCs are transfused within three hours after the Hb transfusion threshold is reached.

Compliance

Potential protocol deviations and violations are reported to the Coordinating Centre within 72 hours and further classified into four categories (Figure 2), reflecting the following situations wherein: i) an RBC transfusion occurred while the Hb threshold is not reached, ii) more than one unit is transfused without reassessing the Hb level between transfusions, iii) the delay between reaching the transfusion threshold and transfusion is greater than three hours or a transfusion never

occurred despite reaching the transfusion threshold, and iv) no transfusion occurred in the context of life-sustaining therapy withdrawal. Using a standard operating procedure, an adjudication committee will determine whether each reported event represents a protocol violation, a protocol deviation, or neither (see Appendix 1).

Cointerventions

No intervention other than the allocated transfusion threshold is protocolized. Standard therapeutic strategies according to the Brain Trauma Foundation guidelines are recommended[10].

Outcome Measures

Our primary and secondary outcome measures are validated in TBI patients and aligned with the Common Data Elements developed by the National Institute of Neurological Disorder and Strokes (NINDS)[22]. All primary and secondary outcomes are assessed centrally by trained research personnel blinded to the intervention to minimize the risk of bias during data collection. We chose a 6-month assessment as it is the most common time frame used in modern TBI trials and corresponds to the plateau phase of recovery[23]. Tertiary outcomes are assessed at participating sites, using standardized definitions (see Appendix 2).

Primary Outcome

We are using the Glasgow Outcome Scale extended (GOSe) to assess neurological outcome at six months[24]. The GOSe scale is reliable, sensitive to change[25 26], and is the most widely used clinical and patient-oriented outcome in this population[27-31]. It comprises eight ranking levels from 1 (death, least favorable outcome) to 8 (upper good recovery, most favorable outcome).

Secondary Outcomes

We are assessing ICU, hospital and 6-month mortality. At six months, we measure the Functional Independence Measure (FIM)[32]. The FIM has been used for over three 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 five cognitive components)[33 34]. Each component is scored on a 7-point scale, with higher scores indicating a greater degree of independence. We also evaluate the quality of life using the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) (generic scale) and the Quality of Life after Brain Injury (QOLIBRI) (TBI-specific scale) questionnaires[35-37]. To evaluate depression, we use the self-reported Patient Health Questionnaire (PHQ-9), which includes nine items that assess the frequency of depressive symptoms in the past two weeks[38].

Tertiary Outcomes

We are capturing the number of RBC units transfused in the ICU, lowest daily Hb, infections, duration of mechanical ventilation, and ICU and hospital length of stay. We are also assessing complications related to transfusion.

Data Collection

At enrollment, the study team collects baseline characteristics, pre-randomization cointerventions and episodes of secondary cerebral injury, which are defined as thresholds at which therapeutic intervention is recommended by practice guidelines[10] (see Table 1 and 2). We also collect time from eligibility to randomization and from randomization to study intervention implementation. Daily, we collect data on secondary injury episodes and cointerventions. At ICU discharge, we collect the length of stay and the duration of mechanical ventilation. At hospital discharge, we collect non-neurosurgical procedures, infections and transfusion reactions that occurred during the

hospital stay, as well as the reports of the brain imaging (computerized tomography [CT] and magnetic resonance imaging [MRI]), length of stay, discharge status and location, documentation of prognostic assessment, justifications provided by clinicians for discontinuing life-sustaining therapies, and occurrence of death by neurological criteria.

Table 1. Schedule of enrollment, interventions, data collection and outcome assessments

	Trauma	ICU	Hospital	6 months
Enrollment				
Eligibility screen		✓		
Informed consent		✓		
Allocation		✓		
Intervention – transfusion strategy				
Liberal (Hb > 100 g/L) or restrictive (Hb > 70 g/L)		✓		
Pre-randomization Data Collection*				
Demographics	✓			
Trauma characteristics	✓			
Physical examination	✓	✓		
Laboratory results	✓	✓		
Secondary insults	✓	✓		
Cointerventions	✓	✓		
Neurosurgical and non-neurosurgical interventions	✓	✓		
Blood product transfusions	✓	✓		
Transfusion reactions	✓	✓		
Daily Data Collection				
Physical examination		✓		
Laboratory results		✓		
Secondary insults		✓		
Cointerventions		✓		
Neurosurgical and non-neurosurgical interventions		✓		
Blood product transfusions		✓		
Transfusion complications	✓	✓		
Protocol deviation/violation		✓		
Trial outcomes				
Primary outcome				
Glasgow Outcome Scale extended				✓
Secondary outcomes				
Mortality		✓	✓	✓
Functional Independence Measure				✓
EuroQoL 5-Dimension 5-Level				✓
Quality of Life after Brain Injury (QOLIBRI)				✓

Patient Health Questionnaire-9				✓
Transfusion complications		✓		
Tertiary outcomes				
Red blood cells transfusion		✓		
Lowest Hb		✓		
Infections		✓		
Length of mechanical ventilation		✓		
Length of stay		✓	✓	

*Performed retrospectively after randomization. Hb, hemoglobin.

Table 2. Secondary cerebral injury definitions

	Definition
Hypoxemia	Oxygen saturation < 90% for ≥ 5 minutes on pulse oximetry
Hypotension	Systolic blood pressure < 90 mm Hg for ≥ 5 minutes
Intracranial hypertension	Intracranial pressure > 25 mm Hg for ≥ 5 minutes
Brain tissue hypoxia	Brain tissue oxygen tension [$PbtO_2$] < 15 mm Hg for ≥ 5 minutes *or* Brain tissue oxygen saturation [$SbtO_2$] > 20% below baseline for ≥ 5 minutes *or* $SbtO_2$ < 60% for ≥ 5 minutes

To limit loss to follow up, we are gathering complete contact information for patients, their family practitioners, and caregivers. Local research coordinators send personalized reminders and confirm upcoming interviews with patients. We use flexible schedules for centralized outcomes assessment. We obtain survival status of patients lost to follow-up from public registries or by reaching the primary care team. In our previous multicenter TBI-Prognosis prospective cohort study, we had no losses to follow-up at six months using those strategies[39].

Data Management

The HEMOTION Coordinating Centre, located at the *CHU de Québec-Université Laval Research Centre* (Québec City, Québec, Canada) oversees the trial coordination. Source documents are kept

at each participating site in locked filing cabinets and offices accessible by the site investigators and their authorized personnel. Coded information is entered in a web-based electronic database and stored at the Ottawa Methods Center at OHRI, which meets Health Canada recommendations and Good Clinical Practice for paper-based and electronic document control system. OHRI personnel have secure access to all trial data, but staff from the Coordinating Centre remain blinded to the intervention allocation.

Sample Size

Our sample size was calculated based on the proportion of patients who will experience an unfavorable outcome (GOSe ≤4)[24 27 28]. Assuming a 40% risk of unfavorable outcome in the control group[27 28], 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 1 error of 5%. Our sample size is conservative as it was based on the simple dichotomous cut-off and most used definition of an unfavorable outcome in TBI using the GOSe. Based on simulated data, a sliding dichotomy approach will increase our ability to observe the planned effect size with 95% power. To account for an estimated 2% dropout rate (consent withdrawals and losses to follow-up) based on observed aggregate rates at the interim analysis, the final sample size was increased to 742[40].

Statistical Methods

All analyses will be performed according to the intention-to-treat principle by biostatisticians blinded to the intervention and reported using 95% confidence intervals. Patient characteristics will be presented with means, medians or proportions, as appropriate. The primary outcome will be presented as quantile-specific odds ratios using a sliding dichotomy approach to account for the

whole ordinal scale. With the sliding dichotomy approach, the point of dichotomy of the GOSe for an unfavorable outcome varies according to the baseline prognostic risk. This approach has been advocated by several trialists[41] and used in recent TBI trials to increase the ability to detect smaller effect size with similar power[27 28]. We will assess the baseline prognosis risk with the externally validated International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic model, which includes admission characteristics (hypoxemia, hypotension, and CT scan and laboratory results)[42]. Patients will be split into a minimum of three quantiles according to their baseline prognostic risk. Patients categorized in the worst predicted prognosis quantile will be considered to have an unfavourable outcome if the 6-month GOSe is ≤ 3 (i.e., death, vegetative state, or lower severe disability). We will use multiple imputation to simulate missing data values using imputation models for independent variables in respective analysis models with the number of imputations corresponding to the fraction of missing data, in line with recommendations[43].

We will perform the following secondary analyses for the primary outcome: per protocol analysis, best case-worst-case scenarios for patients with missing primary outcome, proportional odds analysis (provided the distribution of the GOSe meets the proportional odds assumption[44]), and analysis of the GOSe as a binary variable (GOSe ≤4 vs. > 4) using a Chi-Square test and multivariate logistic regression. In sensitivity analyses, we will compare results generated using multiple imputation to complete case results.

Duration of mechanical ventilation and length of stay will be compared using Cox shared frailty regression to account for the competing risk of mortality[45]. Other secondary outcomes including,

the number of RBC units transfused and the lowest daily Hb, will be compared between groups using generalized linear models with appropriate link functions and conditional distributions.

Subgroup Analyses

We will perform subgroup analyses for our primary outcome according to age, sex, TBI severity (moderate vs. severe), country, presence of heart disease, occurrence of decompressive craniectomy or surgical drainage prior to randomization, and occurrence of transfusion prior to ICU admission. We will use the Instrument to assess the Credibility of Effect Modification ANalyses (ICEMAN) to judge the credibility of apparent effect modification among subgroups[46].

Data Safety and Monitoring

We adopted the Data Safety and Monitoring Committee (DSMC) charter template from the DAMOCLES Study Group (see Appendix 3)[47]. The DSMC includes an international expert in transfusion medicine, a senior biostatistician and epidemiologist, and a neurologist with expertise in neurocritical care. Periodically, the DSMC will independently review reports received directly from the Ottawa Methods Centre, including blinded serious adverse events (SAE) reports, protocol adherence, indicators of trial management (e.g., enrollment, consent). The DSMC will also blindly evaluate the primary outcome at the interim analysis of 50% enrollment using the Haybittle-Peto criterion ($p < 0.001$)[48 49].

Serious Adverse Events

Our rationale for reporting SAE is in agreement with a statement on academic trials in critically ill patients[50]. Several potential SAEs are already reported as outcomes, defined *a priori,* while other

events are commonly 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 that is determined to be directly attributable 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 event that ICU physicians or site investigators label as unexpected will be described fully. These will be collated and submitted to the DSMC.

Data Monitoring

The HEMOTION Coordinating Centre team verifies data entered for completeness and accuracy (e.g., range checks for data value), generate queries and communicate with the sites as required. The frequency of the verifications depends on the site enrollment rates, with high enrolling sites having more than one monitoring visit. We are conducting remote continuous monitoring activities, including monitoring visits (remotely or on-site if required), and will perform a final closeout virtual visit for each site.

Patient and Public Involvement

Representative from Brain Injury Canada, a non-governmental organization whose vision is to promote a better quality of life for people affected by acquired brain injury[51], were involved in the trial design, and are involved in its conduction. Patient and caregiver engagement ensures that our study objectives are tailored to their needs.

Trial Oversight

The HEMOTION Steering Committee is comprised of co-investigators with expertise in TBI and neurocritical care, neurosurgery, hematology, transfusion research, trauma, critical care and large-scale multicentre trials. Knowledge users from various organizations and their representatives are also part of the Steering Committee. These organizations are the *Institut national d'excellence en santé et service sociaux*, Canadian Anesthesiologists Society, Canadian Blood Services, and Brain Injury Canada. We have established an Executive Committee to address day-to-day clinical and methodological issues. The Executive Committee is composed of the three principal investigators and is supported by the project manager and trial coordinator. The HEMOTION trial is being conducted under the auspices of the CCCTG, an inclusive group of healthcare professionals that promotes and assists in the implementation of investigator-initiated, patient-oriented, multicentre research in critically ill patients. The trial is also conducted in collaboration with the Canadian Perioperative Anesthesia Clinical Trials Group and the Canadian Traumatic Brain Injury Research Consortium that was created to enhance collaborations among Canadian scientists working in anesthesiology and perioperative medicine, and on different aspects of the continuum of care of TBI patients, respectively.

ETHICS AND DISSEMINATION

Research Ethics Approval and Consent Process

We obtained approval from the research ethics board prior to the initiation of the trial at each participating centre (see Appendix 4). Since all TBI patients are temporarily unable to provide an informed consent, initial consent is sought from a surrogate decision maker (see Informed Consent Form in Appendix 5). If a surrogate decision maker is not available, a deferred informed consent

approach is used where authorized by the local research ethics board as the research risk to patients is minimal, and the studied transfusion strategies are part of usual care in many centres[12 13] and considered acceptable by clinicians caring for these patients[16 21]. A deferred consent approached has been previously used in RBC transfusion strategy trials with no safety issues[52 53]. Should the patient regain capacity to consent, the consent to continue participation is sought. If the study intervention is suspended for any reason, we pursue data collection unless consent is denied.

Protocol Amendments

All past and future changes to the protocol are approved by research ethics committees prior to implementation. Shortly after the ethics approval was obtained and recruitment began, we amended the protocol to detail one exclusion criteria, modify the size of the permuted blocks used for randomization, specify the number of interim analyses, and shorten the time frame to report protocol violation to the Coordinating Centre (Appendix 6). In the spring of 2022, we implemented additional amendments and increased the sample size to compensate for post-randomization exclusions, consent withdrawals and losses-to-follow-up observed at the interim analysis. We detailed the adjudication process for protocol deviations and violations, corrected some administrative details (number of participating sites and countries, updated references), and modified the prognostic model to be used in the sliding dichotomy analysis.

Confidentiality

Confidentiality is maintained by coded identification, password protected files and websites, locked filing cabinets and offices. Direct identifiers are removed and replaced with a code. Site investigators can re-identify specific patients, if required by authorized persons. The code list is

kept in secured cabinets and offices at each participating site, only accessible by the site investigators and their authorized personnel. Electronic data are physically and virtually secured in the data centre physically located at OHRI.

Dissemination

The findings from this trial will be shared with relevant brain injury organizations and healthcare professionals, through the publication of manuscripts, conference presentations and seminars. Based on the findings, this trial will engage knowledge translation specialists to build an implementation strategy to reach as many stakeholders and members of the medical community as possible, to help reduce transfusion-related practice variation and thereby promote better outcomes for patients with TBI.

Current Trial Status

Recruitment began in September 2017 at the *CHU de Québec—Université Laval* and is currently ongoing at 34 recruiting sites in Canada, the United Kingdom, Brazil and France. The recruitment was initially planned to end in spring 2021. As of March 2022, 75% of the target sample size was achieved. Due to the COVID-19 pandemic and the increase of the sample size, the recruitment is expected to be completed in winter 2023.

Authors' contributions:

AFT, DAF, and FLAU originally designed the trial and drafted the manuscript. LC, MPP, RZ, SE, ABD, TW, DEG, AHK, DS, KEAB, JGB, JCM, DJK, IB, PCH, FLam, OC, MSO, PLB, LM, XN, AR, KK, RG, VL and AFR contributed to the protocol and revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Competing interests:

None declared.

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Figure 1. Flow Diagram

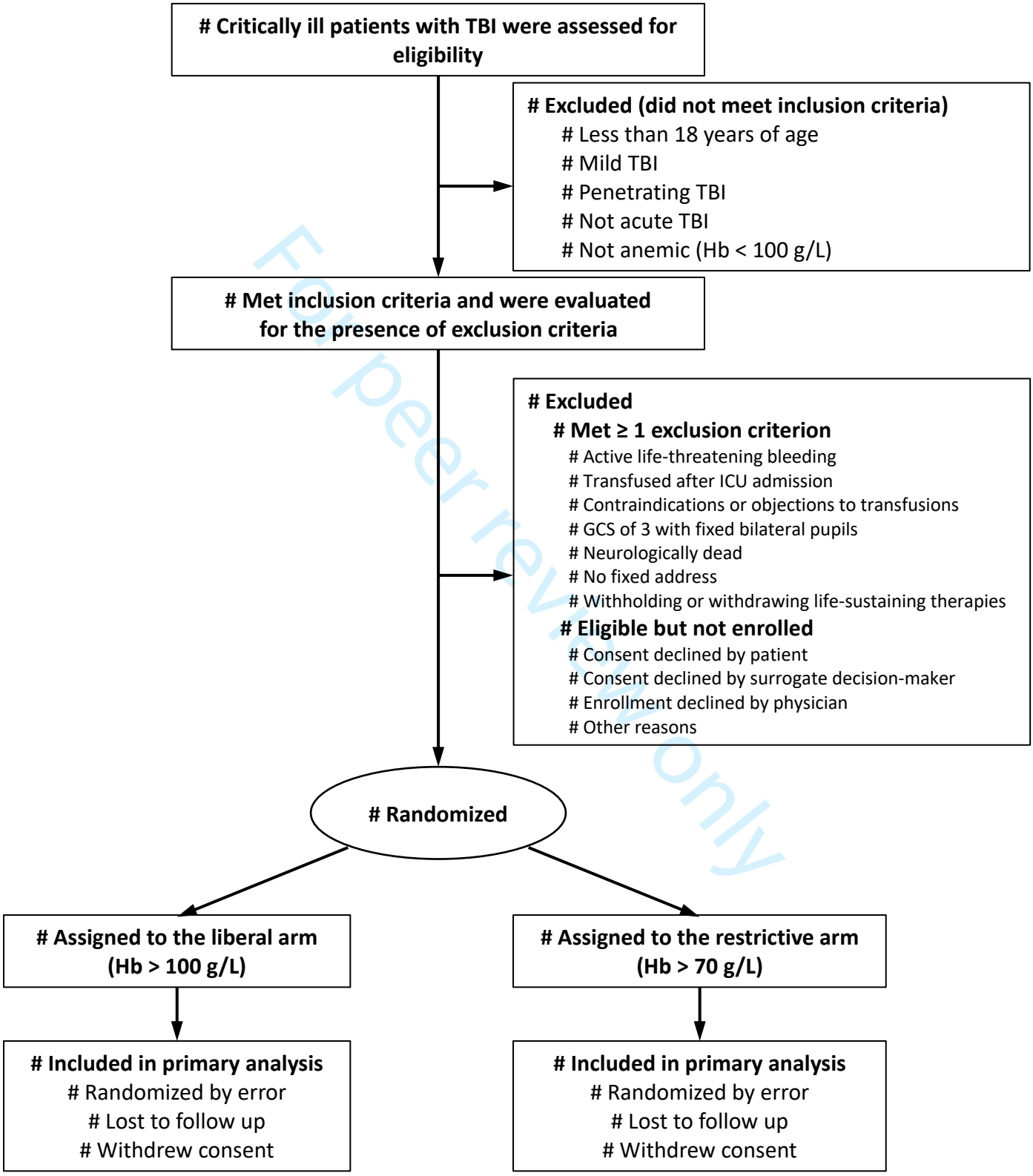
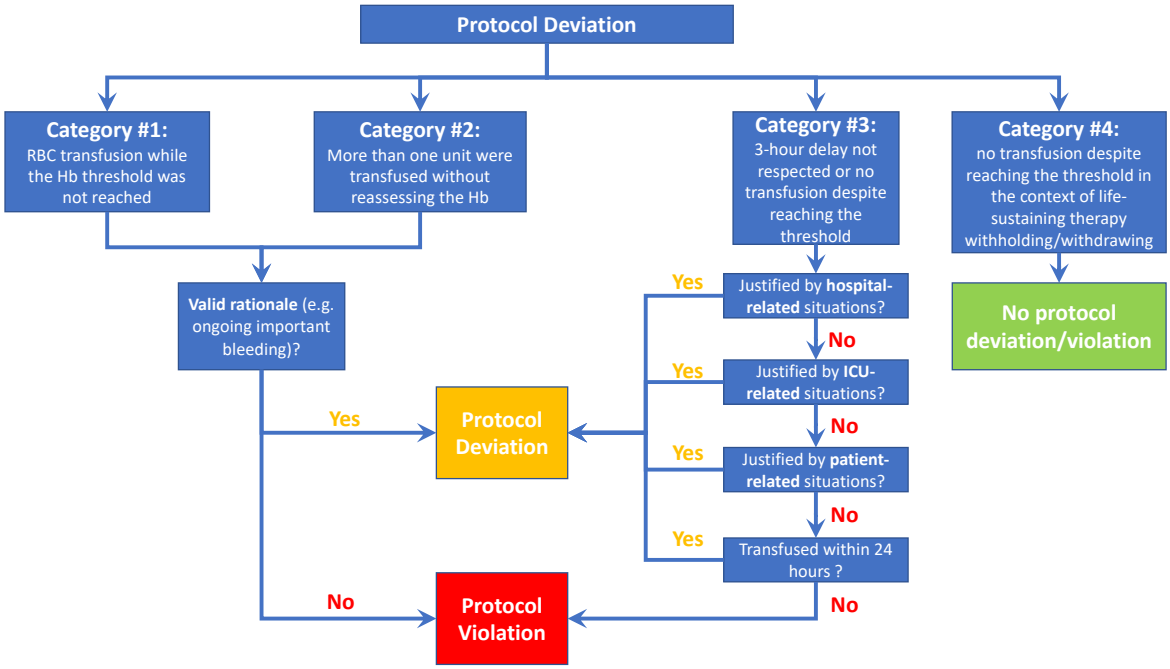


Figure 2. Potential Protocol Deviations and Violations



Appendix 1. Protocol violation adjudication process

Introduction

Adjudication in clinical trials is intended to minimize subjective decisions and systematic errors in the assessment of key information such as patient eligibility, study outcomes and protocol adherence. Evaluating protocol adherence is an important methodological aspect of conducting clinical trials as non-adherence can bias findings. Non-adherent participants may have an inherently different prognosis or be less likely to benefit from (or be harmed by) the study intervention than adherent participants because of suboptimal/sub or supratherapeutic exposure.

No clear, standardized or universal definition of protocol adherence is accepted. As a result, investigators must tailor methods for assessing protocol adherence to the specific characteristics of their trial. This is particularly challenging when the intervention to be tested is complex or involves complex participants and settings such as critically ill patients.

In trials evaluating different hemoglobin (Hb) transfusion thresholds, a clinically significant difference of Hb levels between groups throughout the duration of the intervention is an important objective to demonstrate the fidelity of the interventions and may be considered as the ultimate and true measure of protocol adherence. Since a definitive conclusion on the Hb level difference between groups can only be made at the end of the study, investigators have to monitor, while conducting the study, different parameters to ensure overall adherence.

One critical parameter of protocol adherence is adherence to the transfusion threshold. However, transfusion thresholds need to be contextualized and adapted to the clinical environment, keeping in mind that not all situations in which the transfusion threshold is not respected can be seen as clinically important protocol violations that may bias the results and expose study participants to unnecessary risks. For example, to suspend transfusion in patients for whom a decision to withdraw life-sustaining therapies has been made should not be seen as a protocol deviation or a protocol violation as it represents a judicious use of scarce resources that is unlikely to bias the results.

Some protocol violations are unlikely to have the same impact in a given situation depending on whether it occurs in one study group or another. As an example, transfusing red blood cells (RBC) to a patient allocated to the liberal group while not reaching the transfusion threshold does not have the same impact as transfusing a patient in the restrictive group who did not reach the transfusion threshold. The former situation would result in a greater separation of the Hb curves between study groups while the later would do the opposite. On the opposite, not transfusing a patient of the liberal group who reached the transfusion

threshold would attenuate the difference of the Hb level curves between study groups, while not transfusing a patient allocated to the restrictive group would accentuate this difference.

Another parameter that may be monitored in transfusion threshold trials is the time between reaching the transfusion threshold and administration of the transfusion itself. In patients with traumatic brain injury, the underlying hypothesis of aiming for higher Hb levels is that the injured brain is particularly sensitive to ischemia. Therefore, minimizing the exposure time to low Hb levels may increase the benefits (if any) of targeting higher Hb levels. However, several clinical situations can delay transfusion, such as hospital-related (e.g., rationalization of blood bank services outside of business hours, institutional policy on Hb validation for transfusion), ICU-related (e.g., rationalization of some interventions overnight), or patient-related factors (e.g., difficult crossmatch). These factors are important and may vary across centres, especially in trials conducted in various jurisdictions.

In HEMOTION, we advocate a pragmatic approach where any deviation from the protocol will not be systematically classified as a protocol violation. Instead, deviations will trigger a rigorous and transparent adjudication process whose goal is to systematically assess if each deviation was truly avoidable or clinically important.

Protocol deviations

Protocol deviations will be classified into three categories for review by the adjudication committee:

1. Any situation where RBC transfusion occurred while the Hb threshold was not reached.

2. Any situation where more than one unit were transfused without reassessing the Hb level between transfusion.

3. Any situation where there delay between the Hb measurement and the RBC transfusion is greater than 3 hours or where an RBCs were not transfused despite reaching the transfusion threshold.

If a transfusion is suspended in the context of life-sustaining therapies withholding or withdrawal, this will not be considered as a protocol deviation or violation.

Adjudication process

The protocol violation adjudication committee will consist of two of the principal investigators and three other coinvestigators, including one blood banker, one anesthesiologist and one intensivist. The information to adjudicate the protocol deviations will be extracted from the protocol deviation form. If necessary, additional information will be obtained directly from the research team as per requested by the adjudication committee. We will perform a calibration exercise to reduce the variability in assessments among raters. Independently, all five

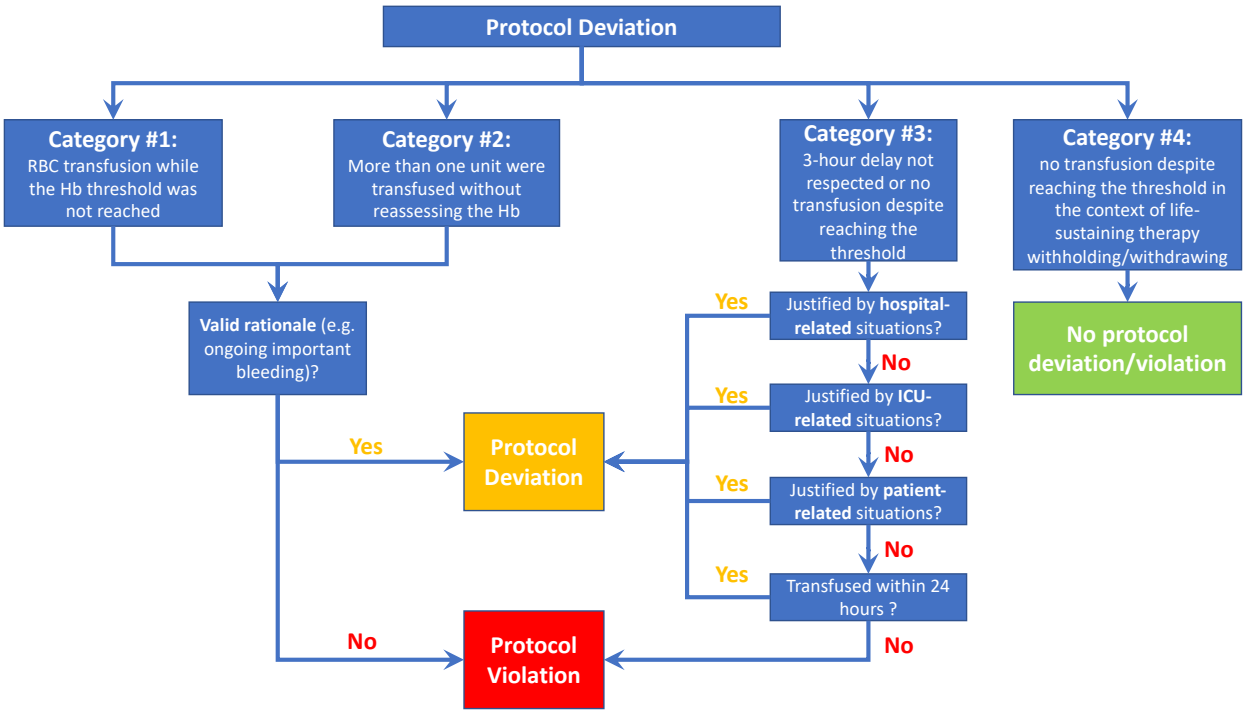
adjudicators will examine 20 *protocol deviations*, including at least three in each of the three above-mentioned deviation category (if the number of deviations per category is sufficient). Adjudicators will discuss their assessments and reasons for disagreement to attempt clarifying the adjudication process. Then, another set of 20 deviations will be evaluated. If the agreement for this set is excellent (kappa greater than 0.8), we will proceed with pairwise adjudication for the remainder of the trial. A pair of adjudicators, including at least one of the principal investigators, will independently assess each event. One of the two principal investigators will be randomly assigned to each deviation and paired with a randomly selected second adjudicator. All adjudicators will be independent and blinded to each other for their initial assessment. Disagreements between pairs of adjudicators will be resolved by further discussion and/or consultation with a third reviewer.

Definition of a protocol violation (see Figure 1)

1. Protocol deviations in which RBC transfusion occurred while the Hb threshold was not reached (**category #1**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or imminent or anticipated Hb drop below the transfusion threshold (e.g., Hb near the transfusion threshold and upcoming major surgery with high risk of bleeding). Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
2. Protocol deviations in which more than one unit were transfused without reassessing the Hb level between transfusion (**category #2**) will be reclassified as a protocol violation if no valid rationale is provided to justify the transfusion. Valid justifications include, but are not limited to, active bleeding or extremely low Hb levels. Adjudicators will then have to classify those events as either **protocol deviation** or **protocol violation**.
3. Protocol deviations in which the three-hour delay between an RBC transfusion and the Hb measurement is not respected will remain classified as a protocol deviation if a valid rationale is provided to justify the delay. Valid justifications can be classified into three different categories (hospital-related, ICU-related, patient-related) and may include (without being limited to) the following scenarios:
    a. Hospital-related situations: rationalization of blood bank services outside of business hours, unavailability of blood due to orange code.
    b. ICU-related situations: rationalization of some interventions overnight due to limited staff issues, another more unstable patient requiring care, institutional policy on Hb validation for transfusion.
    c. Patient-related situations: difficult crossmatch, no IV access available.

    Subsequently, all transfusion delays that are not justified by either those three categories will be reclassified as a protocol violation only if the delay is greater than 24 hours.

Figure 1.



Appendix 2. Tertiary outcomes definition

Acute respiratory distress syndrome: Defined based on degree of hypoxemia: mild (200 mm Hg < $PaO_2/FIO_2 \leq 300$ mm Hg), moderate (100 mm Hg < $PaO_2/FIO2 \leq 200$ mm Hg), and severe ($PaO_2/FIO2 \leq 100$ mm Hg).

Congestive Heart failure (CHF): A documented history of CHF and medications for the treatment of CHF, such as diuretics (i.e., furosemide (Lasix™), +/- ACE inhibitors (i.e., ramipril (Altace™), etc.), or angiotensin 2 receptor blocker (i.e., losartan). Note that the use of these drugs does not necessarily mean that the patient has CHF.

ST elevation MI (STEMI): MI patient with chest discomfort or other ischaemic symptoms that develop ST elevation in two contiguous leads on ECG.

Non-ST elevation MI: MI patient with chest discomfort or other ischaemic symptoms without ST elevation in two contiguous leads on ECG.

Pneumonia (includes hospital-acquired pneumonia and Ventilator associated pneumonia): Definite infection (radiographic evidence of pulmonary abscess and positive needle aspirate OR histological proof on open lung biopsy or at post mortem), probable infection (positive culture of a pathogen known to cause pneumonia from a sputum or endotracheal aspirate specimen, from bronchial washings, bronchoalveolar lavage or bronchoscopy (regardless of quantitation)), possible infection (no microbial confirmation, with a clinical course compatible with hospital-acquired pneumonia and ventilator-associated pneumonia).

Bacteremia: The presence of viable bacteria in the circulating blood detected by hemoculture.

Surgical site infection: (i) Superficial: Within 30 days after surgery AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: a) purulent drainage from the superficial incision, b) organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a microbiological method, c) superficial incision deliberately opened by a surgeon/physician and testing is not performed AND patient has at least one of the following: pain or tenderness, localized swelling, erythema, or heat, d) diagnosis of a superficial incisional surgical site infection. (ii) Deep: Within 30 or 90 days after surgery AND involves deep soft tissues of the incision, AND patient has at least one of the following a) purulent drainage from the deep incision, b) deep incision that spontaneously dehisces or is deliberately opened or aspirated by surgeon/physician and organism identified by microbiological method AND patient has at least one of the following: fever

(>38 °C), localized pain or tenderness, c) an abscess or other evidence of infection involving deep incision detected on gross anatomical or histopathologic exam.

Convulsion/seizure: A seizure is a brief episode that can range from uncontrolled jerking movements (convulsive seizure) to a subtle momentary loss of awareness (absence seizure). Seizures can occur in people who do not have epilepsy for reasons such as brain trauma, drug use, elevated body temperature (febrile seizure), or hypoglycemia.

Meningitis or Ventriculitis: At least one of the following criteria: 1) organism(s) identified from CSF by microbiological method, 2) patient has at least 2 of the following: fever (>38.0 °C) or headache, meningeal signs, cranial nerve signs, AND at least one of the following: a) increased white cells, elevated protein, and decreased glucose in CSF, b) organism(s) seen on Gram stain of CSF, c) organism(s) identified from blood by microbiological method, d) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Brain abcess: At least one of the following criteria: 1) organism(s) identified from brain tissue by microbiological testing method, 2) patient has an abscess or evidence of intracranial infection on gross anatomic or histopathologic exam, 3) patient has at least 2 of the following: headache, dizziness, fever (>38.0 °C), focal neurological signs, altered level of consciousness, or confusion, AND at least one of the following: a) organisms detected on microscopic examination of brain tissue, b) evidence suggestive of infection on imaging test (if equivocal supported by clinical correlation), c) diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for organism.

Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.

Septic shock: A subclass of sepsis where circulatory and cellular/metabolic abnormalities are severe enough (persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg, and with a serum lactate level >2 mmol/L despite volume resuscitation) to substantially increase mortality.

Deep vein thrombosis (proximal DVT): Partially or completely incompressible venous segment of the proximal venous system, assessed at six sites (common femoral, proximal, middle, and distal superficial femoral, and popliteal veins and the venous trifurcation) by Doppler ultrasound. Wall thickening is not diagnostic of DVT.

Pulmonary embolism (PE): Definite (intraluminal filling defect on chest CT scan, a high-probability ventilation-perfusion scan, or autopsy finding), probable (high clinical suspicion and either no test results or nondiagnostic results on noninvasive testing), possible (clinical suspicion and nondiagnostic results on noninvasive testing).

Major bleeding: Defined as hemorrhage occurring at a critical site (i.e., intracranial, pericardial, or retroperitoneal), resulting in hypovolemic shock (i.e., ruptured abdominal aortic aneurysm, upper or lower GI bleed), resulting in the need for a major therapeutic intervention (i.e., surgery), requiring at least 2 units of RBC concentrates, or resulting in death.

Stroke: Poor blood flow to the brain resulting in cell death. There are two principle types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding (or intracranial hemorrhage (ICH)).

Transfusion reactions: The most common complications of transfusions are febrile non-hemolytic reactions, and allergic reactions with urticaria. The most serious complications include an anaphylactic reaction, transfusion-associated cardiac overload (TACO), transfusion-related acute lung injury (TRALI), and acute hemolytic reaction due to ABO incompatibility. Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.

Febrile non-hemolytic reactions:
Fever (> 1 °C with respect to base temperature) with or without shivering at the end of the transfusion or shortly afterwards, that can be accompanied by tachycardia.
- No drop in blood pressure, no lumbar pain, no urticaria, no bronchospasm

Allergic reactions with urticaria:
Urticaria and pruritis at the end of the transfusion, rarely with cough or slight difficulty breathing.
- No drop in blood pressure, no chest tightness, no angioedema

Anaphylactic reaction:
Can happen soon after the start of transfusion. Urticaria, general malaise, chest tightness, edema of the face and glottis, difficulty breathing, drop in blood pressure, bronchospasm.
- Not necessarily with fever initially.

Transfusion-Associated Cardiac Overload (TACO):
Dyspnea during or after the transfusion with tachycardia, crackling sounds at base of lungs ± S3 galop. Sometimes with bronchospasm. Edema/overload on chest X-ray.
- No fever, no drop in pressure, no urticaria.

Transfusion-related acute lung injury (TRALI):
Dyspnea 2–6 h post-transfusion with progressive severe respiratory distress requiring O2 and mechanical ventilation. Diffuse bilateral infiltrations on chest X-ray. Can present with fever and hypotension.

- No urticaria or angioedema. Difficult to distinguish from acute cardiogenic pulmonary edema.

Acute hemolytic reaction due to ABO incompatibility:
Typically 10–20 min after the start of transfusion. Sudden severe malaise with chest tightness, lumbar pain, fever, dyspnea, tachycardia and drop in pressure.
- No urticaria, no angioedema, no bronchospasm, no crackling in lungs on auscultation.

Transmission of infectious organisms (viral, bacterial, prion or parasitic) is also possible.
Note that expected events include transfusion reactions and therefore a transfusion reaction should not be reported as an SAE.

Appendix 3: Data Safety Monitoring Committee Charter

HEMOTION Data Safety and Monitoring Committee Charter

ClinicalTrials.gov Identifier : NCT03260478

Coordinating centre : **CHU de Québec — Université Laval**

Data Management : **Ottawa Hospital Research Center (OHRI)**

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TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

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TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

List of Abbreviations

CHU:	Centre Hospitalier Universitaire
CRF:	Case Report Form
DSMC:	Data Safety Monitoring Committee
PC:	Project Coordinator
PI:	Principal Investigator
REB:	Research Ethics Board
SC:	Steering Committee
TBI:	Traumatic Brain Injury

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

1. HEMOTION trial Organization in Relation to DSMC

The HEMOTION trial DSMC charter is based in part on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter[1]. This charter outlines the roles, responsibilities, timing, frequency and format of meetings, methods of providing information to and from the DSMC, statistical issues, and relationships of the DSMC to the Principal Investigators (PIs) [Alexis F Turgeon, Dean Fergusson and François Lauzier], Project Coordinator (PC), Steering Committee (SC) [see Appendix 1], Trial Statistician, Investigators, Trial Participants, Institutional Research Ethics Boards (REBs), Sponsor [CHU de Québec-Université Laval and Université Laval], Funding Agency [Canadian Institutes of Health Research] and the Canadian Critical Care Trials Group.

2. DSMC Members

The HEMOTION trial DSMC members include: Dr. Darrell Triulzi (University of Pittsburgh), an international expert in transfusion medicine; Dr. Jonathan Cook (University of Oxford), a senior biostatistician and epidemiologist involved in several clinical trials; and Dr. Claude Hemphill (University of California, San Francisco), a neurologist and expert in neurocritical care. The DSMC members are not part of the HEMOTION trial team and were not involved in the development of this proposal.

3. Overview of DSMC Responsibilities

The ongoing primary responsibilities of the DSMC will involve the independent review of reports received directly from the Methods Centre regarding:

1. Recruitment (centre and patient), consent rates and co-enrolment rates
2. Protocol procedures (randomization, protocol violations)
3. Canadian Institutes of Health Research reports
4. Sample data management tables (data completeness, accuracy, timeliness)
5. One interim and final analyses (baseline characteristics, primary, secondary and tertiary outcomes, and serious adverse events)
6. Study metrics at 25, 50 and 75% of enrolment
7. Abstract review

The DSMC will monitor performance and provide suggestions and recommendations as required to protect the validity and credibility of the trial. The DSMC will receive and evaluate all serious adverse events at the time of the interim analyses to safeguard the interest of study participants.

4. Overview of Sample Size Calculation

Our sample size is based on the proportion of moderate and severe TBI patients with an unfavourable outcome (GOSe$\leq$ 4)[2-4]. Assuming a 40% risk of an unfavourable outcome in the restrictive group[3,4], 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 1 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. Our sample size will also allow to detect a 10-point difference on the FIM score with 99% power (assuming a baseline score of 95 and a standard deviation of 10).

5. Overview of Warning Guides

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 $\leq$ 4), and using the sliding dichotomy approach to account for the whole ordinal scale[5]. 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 and used in recent NINDS-funded trials to increase the ability to detect smaller effect size with similar power. We will assess the baseline prognosis risk with the externally validated CRASH prognostic model[6]. Subjects will be split into 6 quantiles 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 $\geq$3. Patients categorized in the best prognosis quantile will be considered to have a favourable outcome if the 6-month GOSe is $\geq$8. 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 (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.

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

The DSMC may or may not consider a significant difference for harm between groups at this interim analysis to be sufficient grounds to recommend suspending enrolment. Other considerations may influence recommendations such as other outcome results, methodological or practical concerns, or external evidence. The DSMC will inform the PIs and SC if, in their view, major safety issues have arisen that are likely to convince a

broad range of clinicians, including those supporting the trial and the general clinical community, that on balance, some aspect of the trial is potentially harmful for all or a particular subgroup of patients.

After the interim analysis, the DSMC will:

1. recommend whether to continue patient enrolment;
2. recommend whether to suspend enrolment until careful review by the PIs and SC;
3. recommend whether more information is required before a recommendation can be made;
4. recommend whether to terminate enrolment.

6. Specific Responsibilities of the DSMC

1. To aid the PIs and SC by providing advice about the conduct of the trial and integrity of the data, so as to protect the validity of the trial, current and future patients.
2. To ensure the overall safety of trial patients by protecting them from avoidable harm.
3. To also review study metrics at 25, 50 and 75% enrolment.

7. Relationship with the Principal Investigators and Steering Committee

1. The DSMC is independent of the PIs and SC in operating and formulating recommendations, but is supportive of the aims and methods of the trial.
2. The DSMC serves in an advisory role to the PIs and SC.
3. The PIs and SC receive DSMC recommendations under advisement.
4. The DSMC, PIs and SC work collaboratively to ensure rigorous, safe and timely conduct of the trial.

8. Initial Responsibilities of the DSMC

1. Review the DSMC Charter and the protocol.
2. Review, discuss, debate and approve the Methods Centre operations.
3. Review, discuss, debate and approve the mechanisms for transmitting serious adverse event information to the DSMC.
4. Establish guidelines for calling emergency meetings of the DSMC.
5. Propose a schedule for subsequent DSMC meetings, acknowledging that the Chair may call for a meeting of the DSMC at any time, as may the PIs.
6. Approve or refine template tables provided by the PIs and Trial Statistician for future review at the interim analyses.

7. Disclose any conflicts of interest such as: current honoraria or consultancies, involvement in regulatory issues relevant to the intervention, investment, enrolment of patients in the trial, strong prior beliefs constituting intellectual conflict, other dual loyalties, etc. Decisions concerning whether an individual with a real or perceived conflict of interest may participate on the DSMC will be made by the DSMC Chair.

9. Ongoing Responsibilities of the DSMC

The DSMC is responsible for helping to ensure that patients in the HEMOTION trial are not exposed to unnecessary or unreasonable risks and that the trial is conducted according to the highest scientific and ethical standards. The DSMC will:

1. Review data from the planned interim analysis provided by the PI and SC.
2. Alert the PIs and SC about scientific, procedural or ethical concerns emerging from the interim analysis and from the final trial results.
3. Provide recommendations to facilitate rigorous, timely completion of the trial.
4. Comment on any new relevant external published data (provided by the PIs and SC) that may impact on patient safety or the efficacy of the study intervention.
5. Provide recommendations for adjustment of the sample size or trial termination.
6. Read and provide suggestions for manuscript publications before submission.
7. Be acknowledged in the main report, unless requested otherwise.

10. Timing of Meetings

The DSMC will meet:

1. Once initially to discuss the protocol and analysis plans, the DSMC Charter, template tables, and to clarify any aspects with the PIs and SC.
2. At the time of the interim analysis.
3. At the end of the trial to allow the DSMC to discuss the final data with the PIs and SC to advise on data interpretation.
4. As needed, in person or by teleconference.

11. Responsibilities of the Principal Investigators and Project Coordinator

1. The PIs and PC will provide the DSMC Charter, protocol and CRFs to the DSMC before the initial meeting.
2. The PIs and PC will provide preliminary template reports of recruitment (centre and patient) and consent rates; procedures (randomization errors, crossovers, protocol adherence, protocol violations); data management (data completeness, accuracy, timeliness and query resolution); physiologic safety data; funding agency reports; one interim and final analyses (baseline characteristics, primary, secondary and tertiary outcomes, and serious adverse events) and abstracts to date.

3. The PIs and SC will modify these template reports as requested to create tables for the interim analysis.
4. For baseline characteristics and outcomes, the Trial Statistician blinded to the group allocation will provide to the DSMC, data according to group A and B, including baseline characteristics (age, sex, TBI severity, etc.), primary, secondary and tertiary outcomes and serious adverse events.
5. The PIs, SC and Trial Biostatistician will ensure that DSMC members remain blinded to allocation.
6. The PIs and SC will provide the results of any new relevant external published data for DSMC consideration.

12. Three-Part Structure of DSMC Meetings

1. First, an open session will be held with the PIs, PC and Trial Statistician. The purpose will be to review accrual, data timeliness and quality, completeness of the follow-up and adjudication, serious adverse events, problems with specific centres, and any proposals for changes in the trial protocol or duration. In addition, the PIs will report any new external evidence (especially results from other relevant ongoing studies) that bear on the conduct of the trial.
2. Second, a partially closed session between the DSMC and the Trial Statistician to review the primary, secondary and tertiary outcomes separated by group and presented in a blinded fashion (group A and group B). These data will not be available to the PI, PC, SC, or Investigators except as authorized by the DSMC Chair. The PIs will receive data in aggregate form.
3. Third, a totally closed session for just the DSMC members to discuss the emerging results, decide on recommendations, and draft comments and recommendations.

13. Potential Unblinding of the DSMC

1. During the closed session, if the DSMC deems it crucial to their interpretation of the data, the DSMC will request unblinding themselves to group assignment without informing the investigative team of this need.
2. The request to unblind would need to be based on findings that are extreme and unambiguous, and the decision of the DSMC to request unblinding should be unanimous.
3. To achieve unblinding, the DSMC will have immediate access to the Data Management personnel at the OHRI Methods Center. An independent statistician will redo analyses if requested. The PI, SC and Trial Statistician will not review the unblinded results.

14. Discussions of the DSMC

1. Efforts should be made for the DSMC to reach unanimous recommendations.
2. The role of the Chair is to summarize discussions and encourage consensus.

3. Before making any recommendations, the DSMC should consider the ethical, scientific, statistical, practical and financial implications for the trial.

15. Minutes of DSCM Meetings

1. Within a week of each DSMC meeting, the Chair will generate minutes of the open and closed sessions of the meeting.
2. The minutes will contain the major points of discussion, recommendations made, and any additional information requested for future meetings.
3. Minutes of the open session of the meeting will be for the PIs, PC and SC.
4. Minutes of the closed session will be for the DSMC members only, until the trial is complete.

16. Reports of the DSMC

1. After each DSMC meeting, the Chair will report to the PIs and SC. Each meeting will be summarized in two reports (one short report suitable for Investigators, the sponsor, REBs and the funding agency) and one more detailed report for the PIs, PC and SC.
2. If accepted by the SC, the PIs will circulate the DSMC's short and long reports to the appropriate personnel.
3. If the DSMC recommends continuing enrolment in the trial following an interim analysis, no other information shall be provided to the PI and SC.
4. If the DSMC recommends suspending enrolment of the trial until a careful review by the PI and SC; or whether more information is required before a recommendation can be made, or whether to terminate enrolment, the DSMC will provide a full report of the rationale to the PIs, PC and SC.

17. Conflict Resolution

1. In the event that the PIs or the SC disagree with the DSMC recommendations to modify or to terminate the trial, a third party arbitrator may be called upon.
2. A third party arbitrator, selected by both parties, will be an individual possessing the requisite knowledge and experience (ideally both methodological and clinical), to make a final decision.
3. The selection of the third party arbitrator will be made by mutual consent of both the PIs and the DSMC Chair.
4. It is the responsibility of the PIs to notify the Investigators, the sponsors and participating REBs of any recommendations about trial modification or enrolment suspension or termination.

18. Confidentiality

1. It is the duty of each member of the DSMC to protect the confidentiality of the trial and the results of monitoring.
2. The members of the DSMC acknowledge that the data emerging from this trial are the collective property of the PI, SC and Investigators.
3. DSMC members will not have the right to present or publish data from this trial anywhere without the explicit permission of the PIs and SC, and not until after the trial is complete.
4. DSMC members will not act as representatives for the study, nor address questions that may arise about the trial.

19. Reporting on the DSMC

1. A brief summary of the roles, responsibilities, and recommendations of the DSMC will be included in the trial manuscript.
2. DSMC members will be invited to read and comment on the trial manuscript, including any statement related to the DSMC.
3. DSMC members will be named and their affiliations listed in the trial manuscript, unless requested otherwise.

20. References

1. DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet.* 2005 ; 365(9460) : 711-722.
2. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1974 ; 2(7872) : 81-84.
3. Nichol A, French C, Little L, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. *Lancet.* 2015 ; 386(10012) : 2499-2506.
4. Wright DW, Yeatts SD, Silbergleit R, et al. Very Early Administration of Progesterone for Acute Traumatic Brain Injury. *N Engl J Med.* 2014:141210140028006.
5. Murray GD, Barer D, Choi S, et al. Design and analysis of phase III trials with ordered outcome scales: the concept of the sliding dichotomy. *J Neurotrauma.* 2005;22(5):511-517.
6. MRC CRASH Trial Collaborators, Perel P, Arango M, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. *BMJ.* 2008;336(7641):425-429.

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

APPENDIX 1. Members of the Steering Committee

Investigators

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

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

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

Algird, Almunder. McMaster University, Hamilton (Ontario), Canada

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

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

Charbonney, Emmanuel. Université de Montréal, Montréal (Québec), Canada

Chassé, Michaël. Université de Montréal, Montréal (Québec), Canada

Docherty, Annemarie. The University of Edinburgh, Edinburgh, United Kingdom

Dubé, Jean-Nicolas. Centre intégré universitaire de santé et de services sociaux de la Mauricie-et-du-Centre-du-Québec, Trois-Rivières (Québec), Canada

English, Shane. Ottawa Health Research Institute, Ottawa (Ontario), Canada

Green, Rob. Dalhousie University, Halifax (Nova Scotia), Canada

Griesdale, Donald. University of British Columbia, Vancouver (British Columbia), Canada

Hébert, Paul. Université de Montréal, Montréal (Québec), Canada

Khwaja, Kosar. McGill University Health Center, Montréal (Québec), Canada

Kramer, Andreas. University of Calgary, Calgary (Alberta), Canada

Kutsogiannis, Jim. University of Alberta, Edmonton (Alberta), Canada

Lamontagne, François. Université de Sherbrooke, Sherbrooke (Québec), Canada

TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

Laroche, Vincent. CHU de Québec-Université Laval, Québec (Québec), Canada

Lessard-Bonaventure, Paule. CHU de Québec-Université Laval, Québec (Québec), Canada

Malbouisson, Luiz. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

Marshall, John. St. Michael's Hospital, Toronto (Ontario), Canada

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

Pili-Flouri, Sébastien. Centre Hospitalier Universitaire de Besançon, Besançon, France

Rigamonti, Andrea. St. Michael's Hospital, Toronto (Ontario), Canada

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

St-Onge, Maude. CHU de Québec-Université Laval, Québec (Québec), Canada

Tinmouth, Alan. Ottawa Hospital Research Institute, Ottawa (Ontario), Canada

Verret, Michaël, CHU de Québec-Université Laval, Québec (Québec), Canada

Walsh, Tim. The University of Edinburgh, Edinburgh, United Kingdom

Zarychanski, Ryan. University of Manitoba, Winnipeg (Manitoba), Canada

Knowledge users

Brain Injury Association of Canada

Canadian Anesthesiologists Society

Canadian Critical Care Trials Group

Canadian Critical Care Society

Institut national d'excellence en santé et services sociaux

Héma-Québec

Appendix 4: List of Research Ethics Boards

Canada

Nova Scotia Health Research Ethics Board
- Queen Elizabeth II Health Sciences Centre

Comité d'éthique de la recherche du CHU de Québec-Université Laval for:
- CHU de Québec – Université Laval (Hôpital de l'Enfant-Jésus)
- Montréal General Hospital
- CIUSS de l'Estrie – CHU de Sherbrooke (Hôpital de Fleurimont)
- CIUSSS de la Mauricie-et-du-Centre-du-Québec (Centre hospitalier de Trois-Rivières)
- Centre Hospitalier de l'Université de Montréal (CHUM)

Ottawa Health Science Network Research Ethics Board (University of Ottawa Heart Institute Panel) for:
- The Ottawa Hospital (Civic Campus)
- Sunnybrook Health Sciences Center
- London Health Sciences Centre
- Hamilton Health Sciences Center
- St. Michael's Hospital
- Kingston General Hospital

University of Manitoba Biomedical Research Board
- Winnipeg Health Sciences Center

Saskatchewan Health Authority Research Ethics Board
- Regina General Hospital

University of Calgary Conjoint Health Research Ethics Board
- Foothills Medical Centre

University of Alberta Health Research Ethics Board (Biomedical Panel) for:
- University of Alberta Hospital
- Royal Alexandra Hospital

Vancouver Island Health Authority Clinical Research Ethics Board
- Victoria General Hospital

UBC Clinical Research Ethics Board
- Vancouver General Hospital

United Kingdom

West Midlands - Coventry & Warwickshire Research Ethics Committee for:

- Salford Royal Hospital
- St. Mary's Hospital (Imperial College Healthcare)
- University Hospital of Wales
- University of Nottingham Hospital
- Royal Stoke University Hospital
- James Cook University Hospital
- The Walton Centre
- Aintree University Hospital

Scotland A Research Ethics Committee Research Ethics Service

- Western General Hospital

France

Comité de Protection des Personnes (CPP) Est 1 for:

- CHU de Clermont-Ferrand
- CHU de Besançon
- Hôpital de Hautepierre
- CHU de Nîmes

Brazil

Comissão nacional de ética em pesquisa provides national REB approval in Brazil

Comitê de Ética em Pesquisa do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo

- The Hospital das Clinicas da Facudade de Medicina da USP

Comitê de Ética em Pesquisa do Hospital de Câncer de Barretos

- Santa Casa de Misericórdia de Barretos

Appendix 5 : Informed Consent Form

Information Sheet and Consent Form

Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Principal Investigators:

Dr Alexis Turgeon
Department of Critical Care Medicine
CHU de Québec — Université Laval

Dr François Lauzier
Department of Critical Care Medicine
CHU de Québec — Université Laval

Dr Dean Fergusson
Clinical Epidemiology Program
Ottawa Hospital Research Institute

Local Investigator LOCAL INVESTIGATOR NAME(S)

Local Co-Investigators: LOCAL CO-INVESTIGATOR NAME(S)

Granting Agency: Canadian Institutes of Health Research

Preamble

We request the participation of the person you represent in a research project. However, before accepting and signing this information sheet and consent form, please take the time to read, understand and carefully consider the following information.

This document may contain words that you do not understand. We invite you to ask any questions you may find useful to the Investigator in charge of this project or to the research staff. You may also ask them

to explain any word or information that is not clear.

Objectives of this Research Project

The person you represent is currently hospitalized in the intensive care unit (ICU) following a traumatic brain injury (TBI). TBI is an important cause of disability and can result in severe sequelae. TBI victims often have low hemoglobin levels (anemia) for a variety of reasons. This low level of hemoglobin can lead to additional sequelae by decreasing oxygen delivery to the brain. Generally, doctors prescribe transfusions of red blood cells (blood transfusion) when the hemoglobin is below 70 g/L to maintain oxygen delivery. However, we ignore if it would not be better to aim for higher hemoglobin levels.

The main objective of this study is to evaluate whether maintaining hemoglobin levels above 100 g/L (rather than 70 g/L) with red blood cell transfusions reduces the sequelae caused by the TBI.

This study will take place in several sites across Canada and the UK and will involve approximately 712 patients. The study will last approximately 4 years.

Procedures of the Research Project

If the hemoglobin level of the person you represent is below 100 g/L, the participant will be randomly assigned (such as flipping a coin) to one of two groups:

A computer will randomly determine in which group the person you represent will be assigned. There will be a 50% chance (1 chance out of 2) to be assigned to one of the following groups:

Group 1: Transfusion of red blood cells if the hemoglobin level is less than or equal to 100 g/L
Group 2: Transfusion of red blood cells if the hemoglobin level is less than or equal to 70 g/L

The study intervention will last until you are discharged from the ICU.

The assignment group will not be communicated to you or to the person you represent.

The medical team may have decided to proceed with a blood transfusion as part of this Research Project before obtaining your consent given the urgent need to maintain proper oxygen transport to the brain. If you refuse to allow the person you represent to continue participating, the decision to transfuse will be left to the ICU team. At any time, the physician of the person you represent may terminate study participation if he/she believes it is in the best interests of the participant.

If the person you represent participates in this study, we will collect information from her/his medical record. Her/his contact information will be provided to the coordinating research team. Six months later, a member of the coordinating research team will get in touch with the person you represent to obtain information on the consequences of the TBI, the level of activity, the mental health and the quality of life. This information will allow to evaluate the effect of the study intervention. This should take about 30 to 45 minutes and will be done by phone call or with electronic questionnaires to be completed online (when possible). It is possible that the person you represent will not be able to answer some of the questions due to her/his condition. In this case, we will ask a representative of the patient (yourself or someone else) to answer the questions on behalf of the patient.

Benefits Associated with the Research Project
The person you represent may benefit from participating in this Research Project, but we cannot guarantee this. However, the results of the Research Project will contribute to the advancement of scientific knowledge and may benefit future patients.

Risks Associated with the Research Project
Most patients with TBI will receive red blood cell transfusions during their hospitalization. In this study, patients allocated to Group 1 may receive more transfusions than patients allocated to Group 2.

The risks incurred by study participants are the same as those incurred by non-study patients receiving transfusions.

The side effects of red blood cell transfusions include:

- Uncommon (fewer than 1%)
  - Fever
  - Skin rash
- Rare (fewer than 0.1%)
  - Serious allergic reaction that may be life-threatening
  - Transfusion reactions associated with red blood cell damage
  - Lung injury
  - Fluid overload in the lungs
- Very rare (fewer than 0.001%)
  - HIV, Hepatitis B, Hepatitis C. The Canadian system of blood collection and distribution is safer than ever, but it will never be possible to ensure that blood transfusion is free of any risk of disease transmission or infection.

Disadvantages of the questionnaires:
It is possible that some questions may make you or the person you represent feel uncomfortable. The questionnaires do not generate any other disadvantage, except the time devoted to them.

Voluntary Participation and Possibility of Withdrawal
Participation in this Research Project is voluntary. You, and the person you represent, are free to refuse to participate. You, and the person you represent, can also withdraw at any time by informing the research team, without providing an explanation.

The decision not to participate or withdraw from this Research Project will have no impact on the quality of the care and services provided to the person you represent. It will not have an impact on your relationship with healthcare providers.

The Investigators, the Research Ethics Committee of the *CHU de Québec - Université Laval* and the Canadian Institutes of Health Research may terminate the participation of the person you represent to this Research Project without consent if new discoveries or data indicates that it is no longer in the best interest of the participant, if the participant is unable to comply with instructions or if there are administrative reasons for abandoning the Project.

However, before the person you represent withdraws from this Research Project, we suggest to, for security purposes, make a final evaluation by phone.

In case of withdrawal, the data and material already collected will nevertheless be retained, analyzed and used if necessary to comply with regulatory requirements and ensure the integrity of the project.

Any new knowledge that may affect your decision or the decision of the person you represent to participate will be immediately communicated to you.

Confidentiality
During this project, the Investigators and their staff members will collect and record information of the person you represent in a research folder. Only information necessary to meet the scientific objectives of the project will be collected.

This information may include information contained in medical records regarding past and present health status, lifestyle, and investigation results, physical examinations and procedures that will be performed during this Research Project. This data will be retained by the Investigators for 10 years.

All information collected is strictly confidential to the extent permitted by the law. The person you represent will only be identified by a code number. The key of the code linking the participant's name to the research folder will be kept by the Investigators.

To ensure the safety of the person you represent, a copy of this Information Sheet and Consent Form will be included in the medical record. Therefore, anyone who has access to the medical record will have access to the information that the document contains.

The local investigator will forward the coded research data on the person you represent to the Principal Investigators or their representatives (coordinating team). Increasingly, the scientific community, the granting agencies and medical scientific journals require that data be stored and made available for secondary review and analyses. For publication purposes the de-identified study data may be shared for re-analyses. Your family member's coded research data may also be transmitted by the principal investigator to other researchers from other institutions for secondary analyses or other research purposes. It will not be possible to identify any individual including yourself in any publication.

For surveillance, control, protection and safety purposes, the research folder and the medical records of the person you represent may be consulted by Canadian (e.g. such as Health Canada) or foreign regulatory bodies, by representatives of the Canadian Institutes of Health Research, by institutional representatives or by the Research Committee. These individuals and organizations all adhere to a privacy policy.

You have the right to consult the research folder of the person you represent to verify the information collected and have it corrected if necessary. However, to preserve the scientific integrity of the project, you may only be able to access some of this information once their participation in the Research Project is completed.

Compensation
There is no financial compensation for participating in this Research Project.

Indemnity in Case of Injury and Participant's Rights
If the person you represent should suffer any prejudice because of any procedure related to this Research Project, all the necessary care and services required will be provided.

By agreeing to participate in this Research Project, you do not waive any right or release the Investigators, the institution and the Canadian Institutes of Health Research from their civil and professional liability.

Contacts

If you have questions about the Research Project or if the person you represent has problems that you believe are related to their participation in the project, you can contact the Local Investigator (TELEPHONE NUMBER), the research team (TELEPHONE NUMBER) or go to the nearest Emergency Room.

If you have any questions about the rights of the person you represent, or if you have any complaints or comments, you can contact the Local Service Quality and Complaints Commissioner of the *CHU de Québec — Université Laval* at 418-654-2211.

Monitoring ethical aspects of the research project

The Research Ethics Board of the CHU de Québec-Université Laval approved this research project and ensures the follow-up for all participating institutions of the health and social services network of the province of Québec.

Consent Form
(Temporarily Incapacitated Adult Participant)

Title of the Research Project: Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Since Mr./Mrs. _____ has been suddenly rendered incapable to consent for the reason identified below, the *Code civil du Québec* authorizes you, as _____ (your relationship with the participant) to consent for the person you represent to participate in this research project.

As soon as Mr. / Mrs. _____ is recovered, we will invite her/him to sign the consent form so that he/she can indicate his/her desire to continue or not to participate in the Research Project.

Reason why the participant cannot consent:

_____

I have read the Information Sheet and Consent Form. The research project and this Information Sheet and Consent Form was explained to me. My questions were answered and I was given the time to decide to participate. After consideration, I consent that the person I represent participates in this Research Project under the conditions defined therein. I also authorize the research team to have access to the medical records of the person I represent.

I authorize the family doctor of the person I represent to be informed of the study participation.

☐ Yes ☐ No

_____
Name of the participant (please print)

_____
Name of the person qualified to give consent for care (relationship with the participant) (please print)

_____ _____
Signature of the person qualified to give consent for care Date

Signature of the person who obtained consent if different from the Local Investigator

I explained the Research Project and the Information Sheet and Consent Form to the person qualified to give consent for care, and I answered the questions he/she asked me.

_____

Name of the person who obtained consent (please print)

_____ _____

Signature of the person who obtained consent Date

Consent Form
(Temporarily Incapacitated Adult Participant who Regained Capacity)

Title of the Research Project: Hemoglobin transfusion threshold in traumatic brain injury optimization: the HEMOTION trial

Your legal representative gave consent for your participation in this study because you were not able to decide due to your health condition. Your condition has now improved. We therefore ask you to decide whether you wish to continue your participation in this study. Your decision is voluntary. This means that the decision belongs to you.

You have read the information provided in this information and consent form and someone has explained to you which procedures of the study will be continued. Your questions were answered at your satisfaction. You believe you have understood all the information related to this study.

Participant Consent

I am now able to make my own decisions and:

_____ (initials) I agree to continue my participation in this study.

_____ (initials) I do not agree to continue my participation in this study. I understand that the data already collected may nevertheless be used for this study to ensure its reliability.

_____
Name of the Participant (please print)

_____ _____
Signature of the Participant Date

Signature of the person who obtained consent if different from the Local Investigator

I certify that the Research Project and this Information Sheet and Consent Form have been explained to the participant. I have answered all the questions and I have made it clear that the participant remains free to terminate his participation, without prejudice.

_____

Name of the person who obtained consent (please print)

_____ _____

Signature of the person who obtained consent Date

Appendix 6 : Protocol Revision History

Version Number	Summary of Revisions Made	Version Date
1.0	n/a	July 11, 2017
2.0	• Addition of the Clinical trials.gov registration number • Correction of typos and wording • Update of the list of abbreviations • Precision regarding one exclusion criteria (fixed bilateral dilated pupils) • Modification to the size of permuted blocks for randomization (4 and 6 instead of 2 and 4) • Update of the list of participating sites and anticipated recruitment rate • Modification of the interim analysis (one analysis at 50% enrolment instead of 2 analyses at one third and two thirds) • Modification of the time frame to report protocol violations at the Coordinating Centre (72 hours instead of 96 hours)	Nov 22, 2017
3.0	• Increase in sample size • Addition of Withdrawal of Life-Sustaining Therapies as a trigger to stop applying the intervention • Addition of the PACT as a collaborative research network • Minor corrections to the text and references • Clarification of secondary and tertiary objectives • Addition of patient minimum age • Clarification of potential protocol violation definitions and management • Precision regarding the start and end of treatment strategy • Modification of the list of participating centres • Increase in recruitment period • Precision on required imaging results • Deletion of one secondary outcome (return to work) • One secondary outcome changed to tertiary outcome (complications related to transfusion) • Modification of the statistical and analytic plan for the primary outcome, of subgroup and sensitivity analyses • Modification to how follow-ups are organized • Update of References • Update of Steering Committee members and Knowledge users	May 17, 2022

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 9
	2b	All items from the World Health Organization Trial Registration Data Set	1 to 24
Protocol version	3	Date and version identifier	Appendix 4
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	3, 4
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18, 23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18, 17, appendix 3

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8, 9
	6b	Explanation for choice of comparators	11
Objectives	7	Specific objectives or hypotheses	9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12, 13, table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13, 14, table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14, 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	18, 19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10, 14, 15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12, 15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12, 13, 14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13, 14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15, 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17, appendix 3
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17, appendix 3
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Appendix 3
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20, 21_
	31b	Authorship eligibility guidelines and any intended use of professional writers	20, 21, 22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20, 21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.