HEMOglobin transfusion threshold in Traumatic brain Injury OptimizatioN: Statistical Analysis Plan

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Section 1: Administrative Information

1.1 Synopsis

Date	**February 22, 2024**
Study Title	*Hemoglobin transfusion threshold in traumatic brain injury optimization (HEMOTION)*
Study Registration Number	*NCT03260478*
Statistical Analysis Plan (SAP) Version Number	*Version 1.1*
Protocol Version and Date	*Version 3.0*, May 17, 2022 Refer to: Turgeon AF, et al. BMJ Open 2022;12:e067117. doi:10.1136/bmjopen-2022-067117
Trial Statisticians	Xavier Neveu
Trial Principal Investigators	Alexis Turgeon (*corresponding principal investigator)* Dean Fergusson François Lauzier
SAP Authors	Alexis Turgeon François Lauzier Dean Fergusson Peter Greestreet Tim Ramsay Xavier Neveu Lynne Moore

1.2 Revision Control

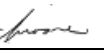
Protocol Version	Updated SAP version number	Section number changed	Description of change	Date changed
3.0	1.0			
3.0	1.1*	6.2	Clarification that the analyses for the primary outcome will be adjusted for sex as for all secondary analyses	February 22nd, 2024
		6.2.3	Clarification that the median difference with 95% CI will be performed using quantile regression models	
		Table 1	Modification of the legend to reflect these clarifications	

*These points required clarification and do not represent a change in the analysis plan. The clarifications were made before the randomization code was opened.

1.3 SAP Signatures

SAP Version Number being approved: 1.1
I approve the attached SAP entitled *HEMOTION* dated <February 22, 2024>

Trial Statistician
Name: Xavier Neveu Signature: 
Date: February 22, 2024

Senior Statistician
Name: Lynne Moore Signature: 
Date: February 22, 2024

Senior Statistician
Name: Tim Ramsay Signature: 
Date: March 4, 2024

Post-doctoral student in biostatistics
Name: Peter Greestreet Signature: 
Date: March 4, 2024

Trial Principal Investigator (corresponding)
Name: Alexis Turgeon Signature: 
Date: February 22, 2024

Trial Principal Investigator
Name: Dean Fergusson Signature: 
Date: March 4, 2024

Trial Principal Investigator
Name: François Lauzier Signature: 
Date: February 29, 2024

1.4 Roles and responsibilities

Name	Role	Institution
Xavier Neveu *TBD*	*Trial Statistician blinded to the treatment allocation (for primary and secondary outcome analyses)* *Statistician not blinded to the treatment allocation (for tertiary outcome analyses)*	*Université Laval*
Alexis Turgeon *Dean Fergusson* *François Lauzier*	*Trial Principal Investigator - corresponding* *Trial co-Principal Investigator* *Trial co-Principal Investigator*	*Université Laval* *University of Ottawa* *Université Laval*
Peter Greestreet	*Post-doctoral student in biostatistics*	*Ottawa Hospital Research Institute*
Tim Ramsay *Lynne Moore*	*Senior Statisticians*	*Ottawa Hospital Research Institute* *Université Laval*

1.5 Contributions

Alexis Turgeon, François Lauzier, Dean Fergusson, Lynne Moore, Peter Greestreet and Tim Ramsay developed the statistical analysis plan (SAP) based on the analyses set out in the trial protocol. Xavier Neveu is the trial statistician and helped answer questions related to trial data and management relevant to the development of the SAP. Alexis Turgeon, François Lauzier, Dean Fergusson and Lynne Moore reviewed, and approved the SAP.

1.6 Abbreviations

- CI – Confidence interval
- CT – Computed Tomography
- DSMC – Data Safety and Monitoring Committee
- EQ-5D-5L – EuroQoL 5-Dimension 5-Level
- EQ-VAS – Visual Analogue Scale of the EuroQoL questionnaire
- FIM – Functional Independence Measure
- GCS – Glasgow Coma Score
- GOSe – Glasgow Outcome Scale extended
- Hb – Hemoglobin
- HR – Hazard ratio
- ICU – Intensive Care Unit
- MICE – Multivariate Imputation by Chained Equations
- OHRI – Ottawa Health Research Institute
- OR – Odds ratio
- PHQ-9 – Patient Health Questionnaire-9
- QOLIBRI – Quality of Life after Brain Injury
- RBC – Red Blood Cell
- RR – Risk ratio
- SAE – Serious Adverse Events
- SAP – Statistical Analysis Plan
- TBI – Traumatic Brain Injury
- tSAH – traumatic Subarachnoid Hemorrhage
- VAS – Visual Analogue Scale

Section 2: Introduction

2.1 Background and Rationale

Traumatic brain injury (TBI) is the leading cause of mortality and long-term disability in young adults[1]. Despite the high prevalence of anemia and red blood cell transfusion in patients with TBI, the optimal hemoglobin (Hb) transfusion threshold is unknown[2]. We undertook a randomized trial to evaluate whether a liberal transfusion strategy improves clinical outcomes compared with a restrictive strategy.

2.2 Objectives

Primary objective:
To evaluate the effect of liberal (experimental) against a restrictive (control) red blood cell (RBC) transfusion strategy using the Glasgow Outcome Scale extended (GOSe) to assess neurological outcome at 6 months. GOSe comprises eight ranking levels from 1 (death, least favourable outcome) to 8 (upper good recovery, most favourable outcome)[3].

Secondary objectives:
To evaluate the effect of transfusion strategies on functional outcome, quality of life, depression and mortality.

Tertiary objectives:
To evaluate the effect of transfusion strategies on the incidence of transfusion-related complications, infections, Hb levels, number of RBC units transfused, and length of stay in the hospital and the intensive care unit (ICU).

Section 3: Study Methods

3.1 Trial Design

HEMOTION is a pragmatic, parallel group, multi-centre, open label blinded-endpoint, randomized trial[4]. Once reaching a Hb ≤100 g/L and after a site investigator has confirmed eligibility, participants will be randomly allocated to either a liberal (experimental) or a restrictive (control) RBC transfusion strategy. The trial intervention is initiated within 3 hours in patients meeting the threshold for transfusion in their respective group. 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. Tertiary outcomes are assessed at participating sites, unblinded to the intervention but using standardized definitions.

The control strategy: Patients in the restrictive transfusion strategy group receive an RBC transfusion only if their Hb is ≤70 g/L.
The experimental 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, is considered acceptable by clinicians caring for critically ill patients with neurological injuries.

3.2 Randomization

Patients are randomized by the research coordinator using 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 Ottawa Methods Centre of the Ottawa Health Research Institute (OHRI) who are not involved in the trial implementation generated the randomization sequence. Analysis of the primary and secondary outcomes will be done by biostatisticians blinded to the intervention. They will also carry out analyses of tertiary outcomes that can be performed without unblinding (i.e., infections, length of stay). Analyses of other tertiary outcomes that require unblinding or will inevitably lead to unblinding (i.e., transfusion-related complications, Hb levels, number of RBC units transfused) will be done by independent biostatisticians not involved in the blinded analyses of other outcomes.

3.3 Sample Size

The sample size was calculated based on the proportion of patients who will experience an unfavourable outcome (i.e., GOSe ≤4, which corresponds to upper severe disability). Assuming a 40% risk of unfavourable outcome in the control group[5,6], a sample size of 712 patients was originally estimated to detect an absolute risk reduction of 10% with a power of 80% and a type 1 error of 5%. This sample size calculation was conservative as it was based on the most widely-used definition of an unfavourable outcome in TBI using a simple dichotomous cut-off of the GOSe. Based on simulated data, the sliding dichotomy analysis is expected to increase the ability to observe the planned effect size with 95% power[7]. Initially, we had not adjusted the sample size for dropouts, given our experience with the prospective observational TBI-Prognosis study, where we did not encounter loss to follow-up when measuring a similar outcome using the same schedule.

3.4 Framework

We hypothesize that a liberal transfusion strategy, compared to a restrictive strategy, will improve 6-month neurological outcomes of critically ill patients admitted to the ICU following a moderate or severe TBI. We therefore use a superiority framework.

3.5 Statistical Interim analyses and stopping guidance (if applicable)

In 2022, a planned interim analysis of the primary outcome was conducted at 50% of enrollment. The data was tested using the Haybittle-Peto criterion ($p<0.001$). At this point, the Data Safety Monitoring Committee considered there was not enough evidence to stop the trial for efficacy (see Appendix 1). Considering the use of the Haybittle-Peto criterion, the final analysis of the primary outcome will be conducted at $p<0.05$. 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, using the formula proposed by Lachin ($N = n/(1-\%)^2$)[8], where n is the original sample size, % is the proportion of dropouts, and N the new sample size).

3.6 Timing of final analysis

The trial is due to finish with the last 6-month follow-up assessment (scheduled in fall 2023, as the last patient was enrolled on April 13, 2023). The statistical analysis plan will be made public before the database is cleaned, verified, and definitively locked. Final analysis will be commenced once the final lock has been confirmed by the principal investigators.

3.7 Timing of outcome assessment

Primary outcome:

- GOSe [6 months]

Secondary outcomes:

- Mortality [In the ICU, in hospital and at 6 months]
- Functional Independence Measure (FIM) [6 months]
- EuroQoL 5-Dimension 5-Level (EQ-5D-5L) [6 months]
- Quality of Life after Brain Injury (QOLIBRI) [6 months]
- Patient Health Questionnaire-9 (PHQ-9) [6 months]

Tertiary outcomes:

- Red blood cell transfusion [In the ICU]
- Lowest Hb [In the ICU]
- Infections [In the ICU]
- Length of mechanical ventilation [In the ICU]
- Length of stay [In the ICU and in the hospital]
- Transfusion complications [In the ICU]

A +/- 2-week time window was allowed for the assessment of the primary and secondary outcomes.

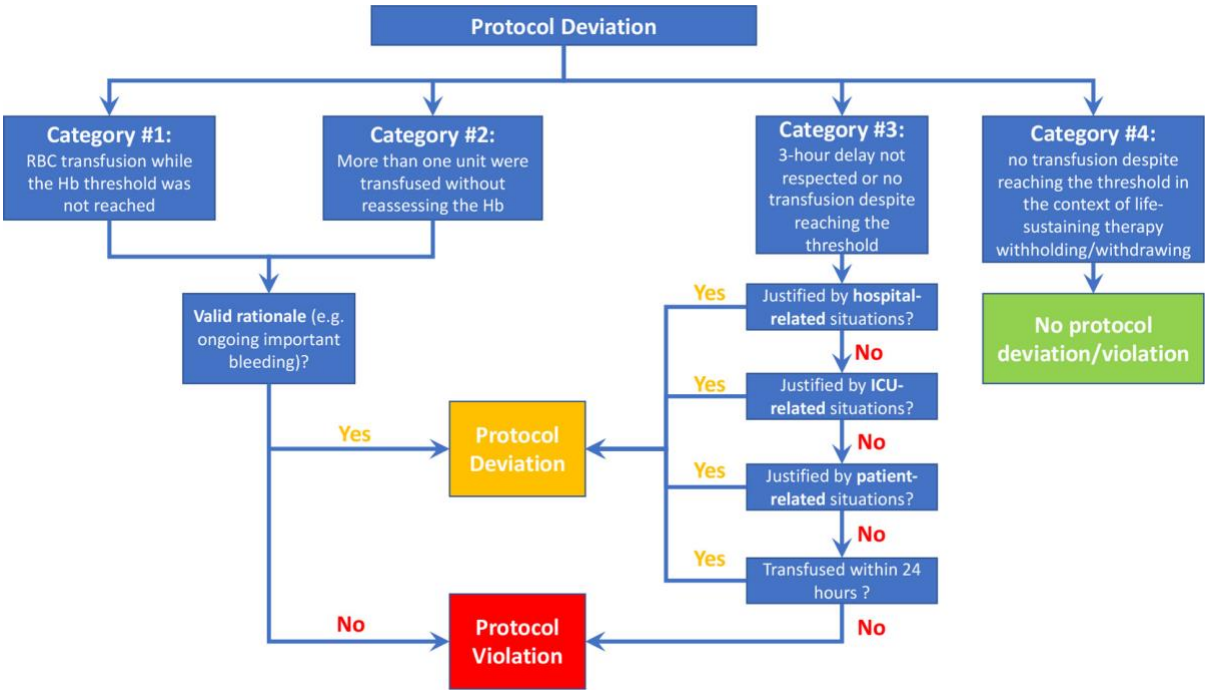
Section 4: Statistical Principles

4.1 Confidence Intervals and P-values

The statistical uncertainty of all point estimates for the primary and secondary outcomes will be expressed as two-sided 95% confidence intervals (CI). The treatment effects for all outcomes will be tested at a 0.05 level of significance.

4.2 Adherence and protocol deviations

Potential protocol deviations and violations are reported to the Coordinating Centre within 72 hours and further classified into four categories (figure below), reflecting the following situations wherein: (1) an RBC transfusion occurred while the Hb threshold is not reached, (2) more than one unit is transfused without reassessing the Hb level between transfusions, (3) the delay between reaching the transfusion threshold and transfusion is greater than 3 hours or a transfusion never occurred despite reaching the transfusion threshold and (4) no transfusion occurred in the context of life-sustaining therapy withdrawal. Using a standard operating procedure detailed in the Study Protocol version 3.0, an adjudication committee will determine whether each reported event represents a protocol violation, a protocol deviation or neither.



4.3 Analysis populations

Intention-to-treat population. This population includes all randomized TBI patients except those who withdrew consent or were lost to follow-up. Baseline characteristics for the intention-to-treat population will be reported in the main manuscript.

Per-protocol population: This population includes all patients within the intention-to-treat group, except those who were allocated to the liberal strategy but were not transfused within a 24-hour time window after reaching Hb ≤100 g/L (protocol violation category #3), and those who were allocated to the restrictive strategy but were transfused despite not reaching their transfusion threshold of ≤70 g/L, or received more than one unit without reassessing the Hb despite the absence of ongoing important bleeding (protocol violation category #1 and 2). Baseline characteristics for the per-protocol population will be reported in an online Supplementary Appendix.

For the patients included and excluded from the per-protocol population, the median time to transfusion and the mean pretransfusion Hb level will be reported according to the treatment allocation.

Section 5 – Trial Population

5.1 Eligibility

Inclusion Criteria:
Subjects must meet all inclusion criteria to participate in this study.

- 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) blunt TBI.
- Hb level ≤100 g/L.

Exclusion Criteria
Subjects meeting any of the exclusion criteria are excluded from study participation.

- Receive transfusion after ICU admission.
- Have contraindications or known objection to transfusions.
- Have no fixed address.
- Patients who meet the criteria for neurological determination of death.
- Those with a GCS of 3 in combination with bilateral fixed dilated pupils at the time of randomization.
- Those with active life-threatening bleeding associated with hemorrhagic shock at the time of randomization.
- Patients for whom a decision to withhold or withdraw life-sustaining therapies has been made at the time of screening.

5.2 Withdrawal/Follow-up

The loss to follow-up rate is expected to be very low[9]. When a patient is lost to follow-up, the 6-month GOSe will be missing, therefore, this patient cannot be included in the analysis of the primary outcome. Whenever possible, such patients will be included in the secondary and tertiary outcome analyses.

No data will be analyzed for patients who withdraw consent, but such patients will be listed in the CONSORT diagram.

5.3 Baseline Patient Characteristics

Baseline characteristics that will be reported are detailed in Appendix 2. To optimize the presentation of categorical variables, categories with less than 5% participant proportion will be merged with the next adjacent category. Further characteristics may be included, and adjustments can be made to the report format in order to meet editorial guidelines.

Section 6 – Analysis

6.1 Outcome Definitions

6.1.1 Primary outcome

- A sliding dichotomy of the GOSe will be used to assess neurological outcome at 6 months[10]. The GOSe comprises eight ranking levels from 1 (death, least favourable outcome) to 8 (upper good recovery, most favourable outcome)[3]. The sliding dichotomy approach will be based on the International Mission for Prognosis and Analysis of Clinical Trials in TBI (TBI-IMPACT) Core+CT+Lab prognostic model[11], which includes the following admission characteristics: age, motor score, pupils, hypoxemia, hypotension, computed tomography (CT) scan classification as defined on the Marshall scale[12], traumatic subarachnoid hemorrhage (tSAH) and epidural mass on head CT scan[13], glycemia and Hb. Head CT scans results will be adjudicated centrally, using the worst results within the first 24 hours following the injury (see Appendix 3). For the motor score, we will use the score at emergency department discharge or the score prior to intubation when the patient was intubated in the emergency department. If no motor score was recorded in the emergency department, we will use the first score recorded upon hospital admission, as recommended[14]. Hypoxemia and hypotension were recorded in the emergency department, using standardized definitions[4]. For glycemia or Hb, we will use the worst value recorded in the emergency department and, when unavailable, the worst value recorded upon admission. Our approach to handling missing data is outlined in section 6.3.

  Patients will then be split into 3 tertiles based on their predicted risk of unfavourable outcome (mortality/vegetative state/severe disability) at 6 months. Patients categorized in the low-risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤5 (i.e., death, vegetative state, lower and severe disability, or lower moderate disability). Patients in the intermediate risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤4 (i.e., death, vegetative state, or lower and severe disability). Patients in the high-risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤3 (i.e., death, vegetative state or lower severe disability).

6.1.2 Secondary outcomes

- All-cause mortality at ICU discharge, at hospital discharge, and at 6 months.
- Functional independence will be assessed using the FIM. This scale evaluates the amount of assistance required to perform 18 basic daily activities (13 physical and five cognitive components)[15]. Each component is scored on a 7-point scale. The final score ranges from 18 to 126, where 18 represents complete dependence and 126 represents complete independence. Deceased patients will be removed for the main analysis.
- Quality of life will be assessed using the Visual Analogue Scale (VAS) of the EQ-5D-5L questionnaire[16]. The EQ-VAS is a generic self-assessment instrument for health-related quality of life, for which zero and 100 represent the worst and best imaginable state of health, respectively. Deceased patients will be removed for the main analysis.

- Quality of life will also be assessed using the QOLIBRI questionnaire[17]. The scores are reported on a 0-100 scale, with zero being the worst possible quality of life and 100 being the best possible quality of life. Deceased patients will be removed for the main analysis.
- Depression will be assessed using the self-reported PHQ-9[18], which includes nine items that assess the frequency of depressive symptoms in the past 2 weeks. The score lies between zero and 27 with zero being the best outcome and 27 the worst. A threshold value ≥10 is generally accepted as the standard for identifying major depression[19]. Deceased patients will be removed for the main analysis.

6.1.3 Tertiary outcomes

- The number of red blood cell units transfused in the ICU.
- The lowest daily Hb level recorded in the ICU.
- Infections categorized as any infection, pneumonia, bacteremia, sepsis/septic shock, central nervous system infection. Both the proportion of patients who had an infection and the proportion of patients who had each category of infection.
- The length of time spent on mechanical ventilation in the ICU.
- The length of stay in the ICU.
- The length of stay in the hospital.
- Complications of red blood cell blood transfusions.

6.2 Analysis Methods

All analyses will be performed using the intention to treat principle (see Section 4.3). The main analysis for the primary and secondary outcomes will be adjusted for sex. It will also be adjusted for site, as there are expected variations in TBI mortality between centers, which may be explained in part by regional variations in approaches to discontinuation of life-sustaining therapies[20]. All treatment effects and differences between groups will be reported with their corresponding 95% CIs. Analyses are summarized in Table 1 and will be reported as outlined in Appendix 2.

6.2.1 Primary outcome analysis

6.2.1.1 Main analysis of the primary outcome:

The null hypothesis states that the proportion of patients with an unfavourable outcome at 6 months, based on a sliding dichotomy of the GOSe score, are equal regardless of the RBC transfusion strategy.

For the main analysis, we will use the sliding dichotomy definition of the primary outcome described in section 6.1. The primary outcome will be analyzed using robust hierarchical Poisson regression, with study site modelled as a random intercept. Risk ratios and absolute risk reduction will be reported. We opted for robust Poisson regression[21] rather than logistic regression to avoid reporting odds ratios, which systematically overestimate risk ratios and are frequently misinterpreted by clinicians[22,23]. Our approach to handling missing covariates to determine sliding dichotomy thresholds is outlined in section 6.3. The distribution of GOSe scores will also be presented graphically in the main manuscript (see Figure 1 in Appendix 2); distributions according to each predicted prognosis tertile will be presented in an online Supplementary Appendix.

6.2.1.2 Sensitivity analyses of the primary outcome:

We will evaluate the robustness of our findings for the main analysis of the primary outcome by conducting sensitivity analyses under various methodological assumptions:

- Multiple imputation. We will use Multiple Imputation by Chained Equations (MICE) for missing covariates, as outlined in section 6.3.
- Complete case analysis. We will only include patients for whom no covariates to calculate the TBI-IMPACT prognostic score were imputed using conditional estimation (see section 6.3).
- Per protocol analysis. See section 4.3.
- Best case-worst-case scenario. We will include randomized patients with missing primary outcome due to consent withdrawal or loss to follow-up; patients who were randomized by error will not be included in this analysis. In the best-case scenario, patients with missing primary outcomes will be considered as having a favourable outcome if randomized in the liberal strategy and as having an unfavourable outcome if randomized in the restrictive strategy. In the worst-case scenario, patients with missing primary outcomes will be considered as having an unfavourable outcome if randomized in the liberal strategy and as having a favourable outcome if randomized in the restrictive strategy.

6.2.1.3 Additional analyses of the primary outcome:

We will conduct additional analyses of the primary outcome to further assess the reliability of our results. Missing covariates will be handled as outlined in section 6.3.

- Hierarchical proportional odds analysis. The regression model will be adjusted for site (random intercept), sex and admission covariates used in the TBI-IMPACT Prognostic model (age, GCS motor score, pupils, hypoxemia, hypotension, CT classification, tSAH and epidural mass on CT, glycemia and Hb).
- Robust hierarchical Poisson regression model for a dichotomized primary outcome (i.e., unfavourable outcome if the 6-month GOSe is ≤4). The model will be adjusted for site (random intercept), sex and admission covariates used in the TBI-IMPACT Prognosis model (age, GCS motor score, pupils, hypoxemia, hypotension, CT classification, tSAH and epidural mass on CT, glycemia and Hb).
- Chi-square test for a dichotomized primary outcome (i.e., unfavourable outcome if the 6-month GOSe is ≤4). We will also report a RR.

We will also perform sensitivity analyses of the additional analyses described above (i.e., proportional odds analysis and robust hierarchical Poisson regression model) by including only cases that have no missing covariates (i.e., complete case analysis).

6.2.2 Secondary outcomes analyses

6.2.2.1 Main analyses of the secondary outcomes:

All measures in the main analyses of the secondary outcomes will be adjusted for site (random intercept), sex and admission covariates used in the TBI-IMPACT Prognosis model. We will handle missing covariates as described in section 6.3.

- Mortality in ICU, in hospital and at 6 months will be analyzed using frailty models and hazard ratios (HR) will be reported. We will provide Kaplan-Meier curves.

- The total FIM score as well as Motor and Cognition sub-scores will be compared using linear mixed models. We will report means, standard deviations, and the mean difference between groups. If data is not normally distributed, we will report medians with interquartile ranges and use quantile mixed models[24] to report difference between groups.
- EQ VAS (visual analogue scale) will be compared using linear mixed models. We will report means, standard deviations, and the mean difference between groups. If data is not normally distributed, we will report medians with interquartile ranges and use quantile mixed models to report difference between groups.
- QOLIBRI will be compared using linear mixed models. We will report means, standard deviations, and the mean difference between groups. If data is not normally distributed, we will report medians with interquartile ranges and use quantile mixed models to report difference between groups.
- PHQ-9 will be compared using linear mixed models. We will report means, standard deviations, and the mean difference between groups. If data is not normally distributed, we will report medians with interquartile ranges and use quantile mixed models to report difference between groups. Also, the proportion of patients with major depression, as defined as a PHQ-9 score greater than or equal to 10[19], will be analyzed using robust hierarchical Poisson regression models[21,25] and reported using RR.

6.2.2.2 Sensitivity analyses of the secondary outcomes:

We will evaluate the robustness of our findings for the main analysis of the secondary outcomes by conducting sensitivity analyses including only cases that have no missing covariates (i.e., complete case analysis).

6.2.2.3 Additional analyses of the secondary outcomes:

We will report unadjusted analyses for all secondary outcomes.

6.2.3 Tertiary outcomes analyses

Main analyses:

The analyses of the tertiary outcomes are descriptive and exploratory. We anticipate that many of these outcomes will occur infrequently, limiting our ability to conduct comprehensive multivariate analyses. Therefore, all analyses will be unadjusted and no sensitivity analyses will be conducted.

- The number of red blood cell units transfused per patient in the ICU will be analyzed using Student's t-test. We will report means, standard deviations, between-group difference and 95% CI. If data is not normally distributed, we will use the Wilcoxon rank sum test and report medians with interquartile ranges as well as median difference with 95% CI.
- The mean lowest daily Hb will be graphically displayed with associated 95% CI at each time point.
- The proportion of patients who had infections or transfusion complications will be analyzed using a Chi-square test. We will report an unadjusted RR.
- Duration of mechanical ventilation, as well as the length of stay in the ICU and the hospital, will be analyzed using the Wilcoxon rank sum test and reported with medians and interquartile ranges as well as median difference with 95% CI using quantile regression models.

6.2.4 Subgroup analyses

- We will perform various exploratory subgroup analyses for the primary outcome using the primary analysis strategy described in section 6.2.1.1.
    - Age > 55 years-old versus ≤ 55 years-old. We hypothesize that the liberal transfusion strategy is more effective in improving functional outcome in older patients, as oxygen brain consumption (per unit volume tissue) increases with age[26] and as increased age is associated with worse autoregulation dysfunction[27], which may render brain more susceptible to the effects of anemia and changes in brain oxygen delivery.
    - Female sex versus male sex. We hypothesize that the liberal transfusion strategy is more effective in improving functional outcome in females, as females exhibit a greater response to red blood cell transfusion than males in terms of cerebral oxygenation[28].
    - Moderate TBI versus severe TBI. We hypothesize that the liberal transfusion strategy is more effective in improving functional outcome in patients with severe TBI, as severe TBI patients are at a higher risk of secondary brain injury due to compromised cerebral autoregulation[29,30].
    - Country (Canada, United Kingdom, France, Brazil). We hypothesize no effect modification of a liberal transfusion strategy according to country.
    - Presence versus absence of heart disease prior to admission (congestive heart failure, myocardial infarction, or ischemic heart disease). We hypothesize no effect modification of a liberal transfusion strategy according to heart disease, as a liberal transfusion strategy did not significantly improve clinical outcomes in patients with acute myocardial infarction[31] or stable heart disease[32].
    - Neurosurgical intervention (decompressive craniectomy/surgical drainage) prior to randomization versus no neurosurgical intervention. We hypothesize no effect modification of a liberal transfusion strategy according to neurosurgical intervention.
    - Occurrence of transfusion prior to randomization versus no transfusion. We hypothesize no effect modification of a liberal transfusion strategy according to transfusion prior to randomization.

6.3 Missing Data

First, every attempt will be made to retrieve any missing data. All frequencies of missing data will be reported. We will not impute data for missing outcomes.

For the main analysis of the primary outcome using sliding dichotomy (see section 6.2.1.1), we estimate that for each covariate of the TBI-IMPACT prognosis score, around 1% of observations will be missing. In sliding dichotomy analyses, each participant needs to have a unique TBI-IMPACT prognosis score calculated to evaluate the baseline prognosis. Then, in case of missing variables of the TBI-IMPACT score, we will then perform single imputation by conditional estimation[33].

For the sensitivity and additional analyses (see section 6.2.1.2 and section 6.2.1.3), and for the main analyses of the secondary outcomes (see section 6.2.2.1), we will use multiple imputation to simulate missing values, assuming that the *missing completely at random* or *missing at random* assumptions are plausible[14,34]. We will use MICE using the MI and MIANALYZE procedures in SAS (version 9.4) with the number of imputations corresponding to the fraction of missing data[35].

Imputation models will include all independent and dependent variables in respective analyses models and any auxiliary variables that may explain the mechanism of missing data (e.g., pupillary reactivity of the contralateral eye when the patient has an ocular prosthesis or had eye/eyelid trauma preventing adequate assessment). We will compare the distribution of observed and imputed values to assess the adequacy of the imputation model[36].

6.4 Harms

The Data Safety and Monitoring Committee (DSMC) charter template from the DAMOCLES study group[37] (which is provided in the supplemental online appendix 3 of the protocol) is adopted. 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).

Serious adverse events:
Our rationale for reporting SAE is in agreement with a statement on academic trials in critically ill patients[38]. 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. All these events will be described in the main manuscript.

Section 7 – References

1. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. *NeuroRehabilitation*. 2007;22(5):341-53.
2. Vlaar AP, Oczkowski S, de Bruin S, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med*. 2020;46(4):673-696.
3. Jennett B, Snoek J, Bond MR, Brooks N. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J Neurol Neurosurg Psychiatry*. 1981;44(4):285-93.
4. Turgeon AF, Fergusson DA, Clayton L, et al. Haemoglobin transfusion threshold in traumatic brain injury optimisation (HEMOTION): a multicentre, randomised, clinical trial protocol. *BMJ Open*. Oct 10 2022;12(10):e067117.
5. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014;371(26):2457-66.
6. 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.
7. McHugh GS, Butcher I, Steyerberg EW, et al. A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: results from the IMPACT Project. *Clin Trials*. Feb 2010;7(1):44-57.
8. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Control Clin Trials*. 1981;2(2):93-113.
9. Turgeon AF, Lauzier F, Zarychanski R, et al. Prognostication in critically ill patients with severe traumatic brain injury: the TBI-Prognosis multicentre feasibility study. *BMJ Open*. 2017;7(4):e013779.
10. 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.
11. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med*. 2008;5(8):e165; discussion e165.
12. Marshall L, Marshall S, Klauber M, Clark M. A new classification of head injury based on computerised tomography. *J Neurosurg (Suppl)*. 1991;75:S14–20.
13. Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery*. 2005;57(6):1173-82.
14. Ercole A, Dixit A, Nelson DW, et al. Imputation strategies for missing baseline neurological assessment covariates after traumatic brain injury: A CENTER-TBI study. *PLoS One*. 2021;16(8):e0253425.
15. Keith RA, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a new tool for rehabilitation. *Adv Clin Rehabil*. 1987;1:6-18.
16. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
17. von Steinbuchel N, Wilson L, Gibbons H, et al. Quality of Life after Brain Injury (QOLIBRI): scale validity and correlates of quality of life. *J Neurotrauma*. 2010;27(7):1157-65.
18. Fann JR, Bombardier CH, Dikmen S, et al. Validity of the Patient Health Questionnaire-9 in assessing depression following traumatic brain injury. *J Head Trauma Rehabil*. 2005;20(6):501-511.

19. Negeri ZF, Levis B, Sun Y, et al. Accuracy of the Patient Health Questionnaire-9 for screening to detect major depression: updated systematic review and individual participant data meta-analysis. *BMJ*. 2021;375:n2183.
20. Turgeon AF, Lauzier F, Simard J-F, et al. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *Can Med Assoc J*. 2011;183(14):1581-1588.
21. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-6.
22. Deeks J. When can odds ratios mislead? Odds ratios should be used only in case-control studies and logistic regression analyses. *BMJ*. 1998;317(7166):1155-6.
23. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. *CMAJ*. 2012;184(8):895-9. doi:10.1503/cmaj.101715
24. Geraci M. Linear Quantile Mixed Models: The lqmm Package for Laplace Quantile Regression. *Journal of Statistical Software*. 2014;57(13):1 - 29.
25. Chen W, Qian L, Shi J, Franklin M. Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. *BMC Med Res Methodol*. 2018;18(1):63.
26. Peng SL, Dumas JA, Park DC, et al. Age-related increase of resting metabolic rate in the human brain. *Neuroimage*. 2014;98:176-83.
27. Czosnyka M, Balestreri M, Steiner L, et al. Age, intracranial pressure, autoregulation, and outcome after brain trauma. *J Neurosurg*. 2005;102(3):450-4.
28. Arellano-Orden V, Leal-Noval SR, Cayuela A, et al. Gender influences cerebral oxygenation after red blood cell transfusion in patients with severe traumatic brain injury. *Neurocrit Care*. 2011;14(1):18-23.
29. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke*. 1996;27(10):1829-34.
30. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery*. 1997;41(1):11-7.
31. Carson JL, Brooks MM, Hebert PC, et al. Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. *N Engl J Med*. 2023;389(26):2446-2456.
32. Carson JL, Stanworth SJ, Guyatt G, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. *JAMA*. 2023;330(19):1892-1902.
33. Gravesteijn BY, Sewalt CA, Venema E, Nieboer D, Steyerberg EW, Collaborators C-T. Missing Data in Prediction Research: A Five-Step Approach for Multiple Imputation, Illustrated in the CENTER-TBI Study. *J Neurotrauma*. 2021;38(13):1842-1857. doi:10.1089/neu.2020.7218
34. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17(1):162.
35. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-99.
36. Nguyen CD, Carlin JB, Lee KJ. Model checking in multiple imputation: an overview and case study. *Emerg Themes Epidemiol*. 2017;14:8.
37. Damocles Study Group NHSHTAP. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet*. 2005;365(9460):711-22.
38. Cook D, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic critical care research. *Can Med Assoc J*. 2008;178(9):1181-1184.

Table 1. Overview of the statistical analytic plan

	Main analysis	Sensitivity analyses for the main analysis	Additional analyses	Sensitivity analyses for additional analyses
Primary outcome				
GOSe at 6 months	• Robust hierarchical Poisson regression*, with a random intercept for site, using sliding dichotomy based on the TBI-IMPACT Prognostic model, with simple imputation using conditional estimation for missing covariates, if necessary.	•Multiple imputation using MICE •Complete case analysis† •Per protocol analysis‡ •Best case-worst-case scenario§	• Hierarchical proportional odds¶ • Robust hierarchical Poisson regression with a dichotomized GOSe at ≤4† • Chi-square test with a dichotomized GOSe at ≤4	• Complete case analysis**
Secondary outcomes				
Mortality in the ICU, in the hospital and at 6 months	• Frailty model¶	• Complete case analysis**	• Unadjusted models	-
FIM (total score, motor and cognition sub-scores)	• Linear mixed model¶	• Complete case analysis**	• Unadjusted models	-
EQ VAS	• Linear mixed model¶	• Complete case analysis**	• Unadjusted models	-
QOLIBRI	• Linear mixed model¶	• Complete case analysis**	• Unadjusted models	-
PHQ-9	• Linear mixed model¶ • Robust hierarchical Poisson regression¶, with a dichotomized PHQ-9 at ≥10.	• Complete case analysis**	• Unadjusted models	-
Tertiary outcomes				
Number of RBC units transfused per patient in the ICU	Student's t-test		-	-
Lowest daily Hb	Graphically displayed with 95% at each time point		-	-
Infections and transfusion complications	Chi-square test		-	-
Duration of mechanical ventilation	Wilcoxon rank sum test		-	-
Length of stay in the ICU and in the hospital	Wilcoxon rank sum test		-	-

* Adjusted for sex
† Includes only patients for whom no covariate was imputed using conditional estimation to calculate the TBI-IMPACT prognostic score
‡ This population includes all patients within the intention-to-treat group, except those who were allocated to the liberal strategy but were not transfused within a 24-hour time window after reaching Hb ≤100 g/L, and those who were allocated to the restrictive strategy but were transfused despite not reaching their transfusion threshold of ≤70 g/L, or received more than one unit without reassessing the Hb despite the absence of ongoing important bleeding.
§ In this analysis we will include patients with missing primary outcome due to consent withdrawal or lost to follow-up; patients randomized by error will not be included. In the best-case scenario, patients with missing primary outcome will be considered as having a favourable outcome if randomized in the liberal strategy and as having an unfavourable outcome if randomized in the restrictive strategy. In the worst-case scenario, patients with missing primary outcome will be considered as having an unfavourable outcome if randomized in the liberal strategy and as having a favourable outcome if randomized in the restrictive strategy.
¶ Adjusted for sex and covariates included in the TBI-IMPACT Prognosis model, with a random intercept for site. Missing covariates will be addressed by multiple imputation using MICE.
** Includes only patients for whom sex and other covariates in the TBI-IMPACT Prognosis model were not missing

Appendix 1

April 08, 2022

Dr Alexis Turgeon
Professor, Department of Anesthesiology and Critical Care Medicine
Université Laval, Québec, Québec, Canada

Object: HEMOTION Trial - Interim analysis

Dear Dr. Turgeon,

The DSMC of the trial was presented the interim analysis report on April 04, 2022.

We have since reviewed the DSMC report including the study metrics and the interim analysis at 50% enrollment. Safety data and compliance data were reviewed as part of this report.

The DSMC recommends that the study continues enrollment without changes.

Sincerely,

Darrell J. Triulzi MD
Chair, HEMOTION DSMC

Appendix 2

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Liberal Strategy (N = xxx)	Restrictive Strategy (N = yyy)
Demographics		
Age — yr	99.9±99.9	99.9±99.9
Female sex — no. (%)	xxx (xx.x)	yyy (yy.y)
Race and ethnicity — no. (%)		
Black or African-American		
Asian		
First Nations or Aboriginal		
Hispanic or Latino		
White		
Other/unknown		
Positive qualitative drug screen — no./total no. (%)		
Positive blood ethanol level — no./total no. (%)		
Congestive heart failure — no. (%)		
Ischemic heart disease/myocardial infarction — no. (%)		
Previous traumatic brain injury, including concussion — no. (%)		
Chronic anemia — no. (%)		
Mechanism of injury		
Cause of injury — no. (%)		
Motor vehicle accident		
Pedal cycle, Motorcycle, scooter, or other all-terrain vehicles accident		
Pedestrian injured in transport accident		
Assault		
Other		
Extracranial injury — no. (%)		
Injury Severity Score†		
IMPACT-TBI prognostic model variables		
Moderate traumatic brain injury — no. (%)‡		
GCS motor score— no./total no. (%)§		
None		
Extension		
Abnormal flexion		
Normal flexion		
Localizes or obeys		
Pupil reactivity — no./total no. (%)		
Both		
One		
None		
Hypotension — no. (%)¶		
Hypoxemia — no. (%)‖		
Injury classification on basis of CT imaging — no./total no. (%)**		
I		
II		
III or IV		
V or VI		
Traumatic subarachnoid hemorrhage — no./total no. (%)		
Epidural mass lesion — no./total no. (%)		
Glucose — mmol/L		
Hemoglobin — g/L		
IMPACT-TBI probability of poor outcome at 6 months††		
Secondary insults prior to randomization		

Episode of hypotension prior to randomization — no. (%)
Episode of hypoxemia prior to randomization — no. (%)
Episode of intracranial hypertension prior to randomization — no. (%)
Episode of cerebral hypoperfusion prior to randomization — no. (%)
Episode of brain tissue hypoxia prior to randomization — no. (%)
Laboratory prior to randomization
Hemoglobin — g/L
Time from injury to first hospital admission — days
Median
Range
Time from injury to randomization — days
Median
Range
Intervention prior to randomization
Intracranial pressure monitoring — no. (%)
Invasive brain oxygenation monitoring — no. (%)
Hyperosmolar therapy — no. (%)
Active cooling — no. (%)
Neuromuscular blocking agent — no. (%)
Barbiturates — no. (%)
Neurological procedures prior to randomization
Decompressive craniectomy — no. (%)
Evacuation of epidural hematoma — no. (%)
Evacuation of subdural hematoma — no. (%)
Evacuation of intracerebral hematoma — no. (%)
Red blood cell transfusion prior to randomization
Any transfusion prior to randomization — no. (%)
Median number of units prior to randomization— no. (interquartile range)

* Plus–minus values are means ±SD.

† The Injury Severity Score ranges from 0 to 75, with higher scores indicating greater severity of injury. Data was missing for x patients in the Liberal Strategy Group and y patients in the Restrictive Strategy Group.

‡ Overall scores on the Glasgow Coma Scale (GCS) range from 3 to 15, with lower scores indicating a lower level of consciousness. The overall GCS score is the sum of scores for the motor, verbal, and eye-opening components. Moderate traumatic brain injury corresponds to a GSC score between 9 and 12. The highest GCS recorded at the emergency department (or the last GCS recorded prior to intubation) was used.

§ GCS motor score of 1 indicates that the patient makes no movements to painful stimuli, 2 has extension, 3 has abnormal flexion, 4 has normal flexion, 5 localizes to painful stimuli, and 6 obeys commands.

¶ Hypotension was defined as a systolic blood pressure of less than 90 mm Hg.

‖ Hypoxemia was defined as an arterial or pulse oxygen saturation of less than 90%.

** The Marshall classification is based on a review of the worst head computerized tomography (CT) scans results within the first 24 hours following the injury, with a score of I indicating normal findings, II indicating diffuse injury, III or IV indicating radiologic signs of elevated intracranial pressure, and V or VI indicating a mass lesion greater than 25 mL.

†† IMPACT-TBI prognosis model is validated to predict functional outcome (Glasgow Outcome Scale Extended < 4) of patients with traumatic brain injury and a GCS score < 13. It is adjusted for age, GCS motor score, pupil response, hypoxia, hypotension, CT classification, blood glucose and hemoglobin concentrations upon admission.

Table 2. Analyses of the Primary Outcome.*	**Liberal Strategy (N = xxx)**	**Restrictive Strategy (N = yyy)**	**Treatment Effect (95% CI)†**
Main Analysis — no./total no. (%)			
Sliding dichotomy for unfavorable outcome‡			
Overall	xxx/xxx (xx.x)	yyy/yyy (yy.y)	x.xx (y.yy to z.zz)
Worst predicted prognosis group			—
Intermediate predicted prognosis group			—
Best predicted prognosis group			—
Sensitivity Analyses			
Sliding dichotomy for unfavorable outcome‡			
Complete case analysis§ — no./total no. (%)			x.xx (y.yy to z.zz)
Per protocol analysis¶ — no./total no. (%)			x.xx (y.yy to z.zz)
Best case scenariol — no./total no. (%)			x.xx (y.yy to z.zz)
Worst case scenario** — no./total no. (%)			x.xx (y.yy to z.zz)
Additional Analyses			
Hierarchical proportional odds analysis††			x.xx (y.yy to z.zz)
Death — no./total no. (%)			—
Vegetative state— no./total no. (%)			—
Lower severe disability — no./total no. (%)			—
Upper severe disability — no./total no. (%)			—
Lower moderate disability — no./total no. (%)			—
Upper moderate disability — no./total no. (%)			—
Lower good recovery — no./total no. (%)			—
Upper good recovery — no./total no. (%)			—
Dichotomized unfavorable outcome‡‡			
Robust hierarchical Poisson regression§§			x.xx (y.yy to z.zz)
Chi-square test			x.xx (y.yy to z.zz)

* The Glasgow Outcome Scale extended (GOSe), measured at 6-month, comprises eight ranking levels from 1 (death, least favourable outcome) to 8 (upper good recovery, most favourable outcome). The primary outcome was centrally assessed by blinded trained personnel.

† The treatment effect is a risk ratio unless otherwise indicated. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.

‡ According to a sliding dichotomy of the GOSe. The sliding dichotomy approach is based on International Mission for Prognosis and Analysis of Clinical Trials in TBI (TBI-IMPACT) Core+CT+Lab prognostic model, which includes admission characteristics (age, motor score, pupils, hypoxemia, hypotension, CT classification, traumatic tSAH on CT, epidural mass on CT, glycemia and Hb). When necessary, we used conditional estimation for missing covariates to calculate an individual TBI-IMPACT score for each patient. Patients will be split into 3 tertiles based on their predicted risk of unfavourable outcome (mortality/vegetative state/severe disability) at 6 months. Patients categorized in the low-risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤5 (i.e., death, vegetative state, lower and severe disability, or lower moderate disability). Patients in the intermediate risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤4 (i.e., death, vegetative state, or lower and severe disability). Patients in the high-risk group will be considered to have an unfavourable outcome if the 6-month GOSe is ≤3 (i.e., death, vegetative state or lower severe disability). Analyses are adjusted for sex, with a random intercept for site.

§ The complete case analysis includes only patients for whom no covariate to calculate the TBI-IMPACT prognostic score was imputed using conditional estimation.

¶ The per protocol analysis excludes patients who were allocated to the liberal strategy but were not transfused within a 24-hour time window after reaching Hb ≤100 g/L, and those who were allocated to the restrictive strategy but were transfused despite not reaching the transfusion threshold of ≤70 g/L or received more than one unit without reassessing the Hb despite the absence of ongoing important bleeding.

ǁ In the best-case scenario, patients with missing primary outcomes were considered as having a favourable outcome if randomized in the liberal strategy and as having an unfavourable outcome if randomized in the restrictive strategy.

** In the worst-case scenario, patients with missing primary outcomes were considered as having an unfavourable outcome if randomized in the liberal strategy and as having a favourable outcome if randomized in the restrictive strategy.

†† In this category, the treatment effect is an odds ratio. The regression model was adjusted for sex and covariates included in the TBI-IMPACT Prognosis model (age, motor score, pupils, hypoxemia, hypotension, CT classification, traumatic SAH on CT, epidural mass on CT, glycemia and Hb), with a random intercept for site.

‡‡ Unfavourable outcome if the GOSe is ≤4.

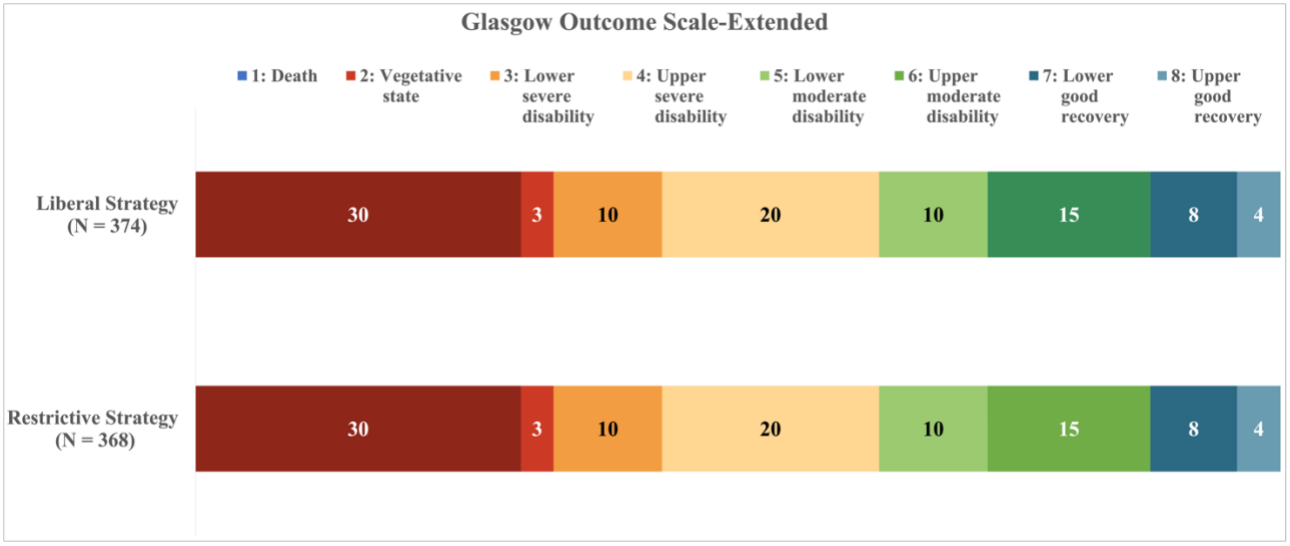
§§ The regression model was adjusted for sex and covariates included in the TBI-IMPACT Prognosis model (age, motor score, pupils, hypoxemia, hypotension, CT classification, traumatic SAH on CT, epidural mass on CT, glycemia and Hb), with a random intercept for site

Table 3. Analyses of the Secondary and Tertiary Outcomes.*

	Liberal Strategy (N = xxx)	Restrictive Strategy (N = yyy)	Treatment Effect (95% CI)†
Secondary Outcomes‡			
Mortality — no./total no. (%)§			
In the ICU	xxx/xxx (xx.x)	yyy/yyy (yy.y)	x.xx (y.yy to z.zz)
In the hospital			x.xx (y.yy to z.zz)
At 6-month			x.xx (y.yy to z.zz)
Functional Independence Measure¶‖			
Overall	999.9±99.9	999.9±99.9	-xx.x (y.y to z.z)
Motor	99.9±99.9	99.9±99.9	-xx.x (y.y to z.z)
Cognitive	99.9±99.9	99.9±99.9	-xx.x (y.y to z.z)
EuroQoL 5-Dimension 5-Level Visual Analogue Scale¶**	99.9±99.9	99.9±99.9	-x.x (y.y to z.z)
Quality of Life after Brain Injury¶††	99.9±99.9	99.9±99.9	-x.x (y.y to z.z)
Patient Health Questionnaire-9¶‡‡	99.9±99.9	99.9±99.9	-x.x (y.y to z.z)
Tertiary Outcomes§§			
Number of red blood cell units transfused per patient¶,¶¶	9.9±9.9	9.9±9.9	-x.x (y.y to z.z)
Infection — no./total no. (%)‖‖			
Any			-x.x (y.y to z.z)
Pneumonia			-x.x (y.y to z.z)
Bacteremia			-x.x (y.y to z.z)
Sepsis/septic shock			-x.x (y.y to z.z)
Ventriculitis/meningitis/brain abscess			-x.x (y.y to z.z)
Transfusion reactions — no./total no. (%)¶,***			-x.x (y.y to z.z)
Median duration of mechanical ventilation — days (interquartile range)¶	9.9 (0.0 to 9.9)	9.9 (0.0 to 9.9)	x.xx (y.yy to z.zz)
Median length of ICU stay — days (interquartile range)¶	9.9 (0.0 to 9.9)	9.9 (0.0 to 9.9)	x.xx (y.yy to z.zz)
Median length of hospital stay — days (interquartile range)¶	9.9 (0.0 to 9.9)	9.9 (0.0 to 9.9)	x.xx (y.yy to z.zz)

* Plus–minus values are means ±SD.
† Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.
‡ Secondary outcomes were centrally assessed by blinded trained personnel. All analyses are adjusted for site (random intercept), sex and admission covariates used in the TBI-IMPACT Prognosis model (age, motor score, pupils, hypoxemia, hypotension, CT classification, traumatic SAH on CT, epidural mass on CT, glycemia and Hb)
§ In this category, the treatment effect is a hazard ratio.
¶ In this category, the treatment effect is the between-group difference.
‖ The Functional Independence Measure scale evaluates the amount of assistance required to perform 18 basic daily activities (13 physical and five cognitive components). Each component is scored on a 7-point scale. The final score ranges from 18 to 126, where 18 represents complete dependence and 126 represents complete independence. Patients who died or with missing data were excluded (xx in the Liberal Strategy and yy in the Restrictive Strategy).
** The EuroQoL 5-Dimension 5-Level Visual Analogue Scale is a generic instrument for health-related quality of life, for which zero and 100 represent the worst and best imaginable state of health, respectively.
†† The Quality of Life after Brain Injury Scale is a TBI-specific instrument for health-related quality of life, for which zero and 100 represent the worst and best imaginable state of health, respectively
‡‡ Patient Health Questionnaire includes nine items that assess the frequency of depressive symptoms in the past 2 weeks. The score lies between zero and 27 with zero being the best outcome and 27 the worst.
§§ Tertiary outcomes were assessed locally by unblinded trained research personnel using standardized definitions.
¶¶ From the randomization to the ICU discharge
‖‖ In this category, the treatment effect is a risk ratio
*** Detailed description of transfusion reactions is provided in the Supplementary Appendix.

Figure 2. Levels on the Glasgow Outcome Scale–extended at 6 Months.



Appendix 3

Interpretation of head CT scans results

We used a rigorous 3-step approach to ensure a robust and unbiased assessment of head CT scans.

Initially, each head CT scan was interpreted by radiologists at participating sites who were unrelated to the research team and unaware of group assignment and clinical outcome of study participants. Subsequent to this interpretation, the local investigator interpreted the CT scan to calculate the Marshall score[12], the Rotterdam score[13] including the presence or absence of epidural hematoma and subarachnoid hemorrhage. The local research team transmitted this information to the coordinating centre.

Given that the local research teams were unblinded to transfusion strategies, all CT reports underwent a second independent analysis by an investigator blinded to group assignment and trial outcomes.

A third adjudication was performed by a second investigator also blinded to the group assignment and trial outcomes. All discrepant interpretations between the site investigator reading and the central adjudication were reviewed independently. If needed, local research teams and the first adjudicator were consulted for clarification. The third adjudication serving as the final decision.