Appendix 3: Data Safety Monitoring Committee Charter

HEMOTION Data Safety and Monitoring Committee Charter

ClinicalTrials.gov Identifier : NCT03260478

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TRANSFUSION IN TRAUMATIC BRAIN INJURY
The HEMOTION TRIAL DSMC CHARTER

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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

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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.

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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.

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20. References

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Canadian Anesthesiologists Society

Canadian Critical Care Trials Group

Canadian Critical Care Society

Institut national d'excellence en santé et services sociaux

Héma-Québec

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