# The POLAR RCT Data and Safety Monitoring Committee Charter

<table>
<thead>
<tr>
<th><strong>Protocol Title:</strong></th>
<th>The prophylactic hypothermia trial to lessen traumatic brain injury (POLAR RCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol Number:</strong></td>
<td>ANZIC-RC/DJC003</td>
</tr>
<tr>
<td><strong>Coordinating Centre:</strong></td>
<td>ANZIC-RC, Monash University</td>
</tr>
<tr>
<td><strong>Data Management:</strong></td>
<td>CCRET, Monash University</td>
</tr>
<tr>
<td><strong>Document Date:</strong></td>
<td>28 May 2015</td>
</tr>
</tbody>
</table>
Contents

1. Introduction ........................................................................................................................................... 3
2. Responsibilities of the DSMC .................................................................................................................. 3
3. Organisational Diagram ......................................................................................................................... 4
4. Membership of the DSMC .................................................................................................................... 5
5. Conflicts of Interest ............................................................................................................................... 6
6. Initial Meeting ......................................................................................................................................... 6
7. Formal Interim Analysis Meetings ........................................................................................................... 6
8. Statistical Monitoring Guidelines .......................................................................................................... 7
9. Additional Safety Data ............................................................................................................................ 7
10. Adverse Event Reporting ...................................................................................................................... 8
11. Serious Adverse Event Reporting ......................................................................................................... 9
12. Procedures to Ensure Confidentiality and Proper Communication .................................................... 11
13. Closed Session ...................................................................................................................................... 11
14. Open Session ....................................................................................................................................... 11
15. Open and Closed Tabulated Data Report ............................................................................................. 12
16. Minutes of the DSMC Meeting ............................................................................................................. 12
17. Recommendations to the Management Committee ............................................................................. 13
1. **Introduction**

This Charter is for the Data and Safety Monitoring Committee (DSMC) POLAR RCT trial, protocol number ANZIC-RC/DJC003.

The Charter will define the primary responsibilities of the DSMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the Closed and Open Report that will be provided by the DSMC.

2. **Responsibilities of the DSMC**

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety during the trial and for monitoring the overall conduct of the clinical trial.

The DSMC will review the trial progress at designated time points and the review will include, but not be restricted to, the following:

- Monitoring evidence for treatment harm (e.g.: SAEs, deaths)
- Assessment of data quality, including completeness
- Monitoring recruitment and losses to follow up
- Monitoring compliance with the protocol
- Monitoring continuing appropriateness of patient information
- Monitoring compliance with previous DSMC recommendations
- Assessing the impact and relevance of external evidence

The DSMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMC may also formulate recommendations relating to the selection/recruitment of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DSMC will be advisory to the POLAR Management Committee (MC), which comprises the clinical trial leadership group. The MC will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.
3. Organisational Diagram

The organisational diagram (Figure 1) shows the relationship between the DSMC and other committees and functional areas involved in the trial.

Figure 1: Organisational diagram
4. Membership of the DSMC

The DSMC is an independent multidisciplinary group who collectively have experience in:

- Management of patients with severe TBI
- Trauma and intensive care research
- Conduct and monitoring of randomised clinical trials
- Human Research Ethics Committees

DSMC Chair:  Prof Jamie Hutchison  
Research Director Critical Care Medicine  
The Hospital for Sick Kids  
Toronto, Ontario, Canada  
jamie.hutchison@sickkids.ca

DSMC Members:  Prof Paul Hébert  
Senior Scientist, Centre de recherche du Centre hospitalier de l’Université de Montréal (CRCHUM)  
Full Professor, Department of Medicine of the Université de Montréal  
Montréal, Canada  
paul.hebert.chum@ssss.gouv.qc.ca

Prof David Zygun  
Professor and Divisional Director, University of Calgary  
Calgary, Alberta, Canada  
dzygun@ualberta.ca

A/Prof Alexis Turgeon  
Associate Professor, Division of Critical Care Medicine, Laval University  
Director of Research for the Division of Critical Care Medicine and the Associate Director of the Population Health and Optimal Health Practices Research Unit of the CHU de Québec Research Centre  
Quebec, Canada  
alexis.turgeon@fmed.ulaval.ca

Prof Dean Fergusson  
Senior Scientist and Director, Clinical Epidemiology Program  
Full Professor, Departments of Medicine, Surgery, and Epidemiology and Community Medicine  
Endowed Chair, Clinical Epidemiology Program  
Ottawa Hospital Research Institute/University of Ottawa  
Ottawa, Canada  
dafergusson@ohri.ca

Statistician:  A/Prof Michael Bailey  
Senior Statistical Consultant, ANZIC-RC, Monash University  
Melbourne, Australia  
michael.bailey@monash.edu
5. Conflicts of Interest

The DSMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Any DSMC member who develops significant conflicts of interest during the course of the trial should resign from the DSMC.

DSMC membership is to be for the duration of the clinical trial. If any members leave the DSMC during the course of the trial, the POLAR Management Committee will promptly appoint their replacements.

6. Initial Meeting

The initial meeting of the DSMC will be held with the DSMC Chair and Principal Investigator(s). It will be held during the final stages of protocol development, to provide advisory review of scientific and ethical issues relating to study design and conduct, to discuss the standard operating procedures for the role and functioning of the DSMC, and to discuss the format and content of the Open and Closed Reports that will be used to present trial results at future DSMC meetings.

The DSMC Chair will be provided with the drafts of the clinical trial protocol, the Statistical Analysis Plan, the DSMC Charter, and the current versions of the case report forms.

7. Formal Interim Analysis Meetings

Two interim analyses are planned for the POLAR trial. This will be performed after enrolment and completion of 6-month follow-up assessments for 125 and 250 patients. Data will be analysed in a blinded fashion initially. Unblinding will occur if safety issues are evident. A teleconference attended by all members of DSMC will be organised as soon as possible after the follow up assessments of the patients group. The DSMC statistician will perform the interim analysis and the results will be forwarded to the DSMC for discussion at a formal closed meeting. A majority decision of the DSMC (≥3:2) will be required to make a recommendation regarding early cessation of the trial. Any proposed modification to the protocol or trial by either the DSMC or MC will be communicated to the respective Chair.
8. Statistical Monitoring Guidelines

Two planned interim analyses are scheduled by the DSMC at six months following 25% (n=125) and 50% (n=250) patient recruitment. There is no plan for early trial stopping for apparent futility.

A group sequential statistical approach will be applied at both interim analyses to assess the trial primary outcome of dichotomized extended Glasgow Outcome Score (GOSE) (or at the discretion of the DSMC, the differential patient mortality) between treatment groups. These interim analyses will use a conventional Haybittle-Peto three standard deviation (|Z_k| ≥ 3) sequential monitoring boundary for efficacy / safety, calculated from a normal approximation to the discrete binomial difference in outcome proportions (approximate P<0.001 in both cases).

At the discretion of the DSMC, comparative treatment group summary information will also be provided for any or all of the adverse events collected in the case report form, as listed below under paragraph 10.

After investigation of whether there appears to be a safety risk at specific centres or across the POLAR centres as a whole, a recommendation to stop the study at specific centres or in its entirety can be made by the DSMC. In these deliberations, the DSMC will be mindful of the specified trial primary outcome, and the implications of multiplicity of statistical testing of trial data for inflation of type I error.

Assuming no early stopping, the negligible effect of the two interim analyses on expenditure of error (final critical value |Z_3| ≥ 1.975 [P value 0.048], rather than 1.960) will allow the final analyses at full recruitment to be little affected by these interim analyses and consequently all final analyses will be conducted with a Type I error alpha equal to 0.05. This level of significance will not be adjusted otherwise for multiplicity; however the primary trial outcome is clearly defined.

9. Additional Safety Data

The DSMC can request additional safety data (documented complications & SAE’s) at other intervals as required.
10. Adverse Event Reporting

An Adverse Event (AE) is an untoward medical event that occurs whilst a patient is enrolled in the study. The following pre-defined adverse events will be recorded in the CRF.

- Bradycardia
- Ventricular tachycardia
- Ventricular fibrillation
- Asystolic or PEA cardiac arrest
- Hypotension (MAP < 60 mm Hg)
- Pneumonia
- Proven bacteraemia
- Cerebral abscess
- CNS infection
- Neurosurgical Wound infection
- Other infection
- New Intra cerebral bleeding
- New significant bleeding
- Intractable Intracranial Hypertension
- Potassium imbalances

Other adverse events that are related to the study treatments will be recorded as free text.
11. Serious Adverse Event Reporting

Serious Adverse Events are defined in the internationally accepted “Note for guidance on clinical safety data management: Definitions and standards for expedited reporting (CPMP/ICH/377/95)” (annotated with TGA comments July 2000) as events or reactions that:

- Result in death
- Are life threatening in the opinion of the responsible investigator
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

For the purposes of this trial adverse events as defined in the CRF will be reported as SAE’s if they fulfil the above criteria.

Determination of SAE’s and AE’s can be assisted by the use of the flow chart (Figure 2). Information about the occurrence of a serious adverse event will be faxed to the Project manager or entered electronically within 24 hours of first knowledge of the event. The Project Manager shall report the SAE’s to the DSMC in tabulated form at 3 monthly intervals. Any recommendations from the DSMC will be disseminated by the Project Manager to other participating sites.

If a SAE is unexpected (ie: not described in the protocol or plain language statement) and thought to be related to study treatment and is “fatal” or “life threatening” the site Principal Investigator must report the event to the Project Manager or designate within 24 hours of knowledge of the event occurring. The Project manager will report such events to the DSMC Chair as soon as possible after receiving notification.

All deaths will be reported as an SAE irrespective of the event leading up to the death.
Figure 2: Serious adverse event reporting flow chart

1. Adverse event
2. Is it related to the study treatment/protocol?
   - Yes
     - Is it associated with a serious outcome?
       - No: Record as an AE
       - Yes: Record as an SAE
   - No
     - Is it associated with a serious outcome?
       - Yes: Record as an SAE
       - No: Do not record as an SAE
12. Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by unidentified treatment group. The trial statistician will be responsible for serving as a liaison between the database and the DSMC. However any interrogation of the database by the trial statistician will be by unidentified treatment group. Temperature data will be analysed separately to ensure that the blinding of results is maintained. The study’s Project Manager will be given immediate access on an ongoing basis to patient-specific information on serious adverse events (SAEs) to satisfy the standard requirement for prompt reporting to the regulatory authorities.

At the same time, procedures will be implemented to ensure proper communication is achieved between the DSMC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for Closed Session and Open Session will be implemented. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues.

13. Closed Session

Sessions involving only DSMC membership (called Closed Sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the safety of interventions. Following the Interim Analysis (Closed Session), the DSMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

14. Open Session

In order to allow the DSMC to have adequate access to information provided by study investigators, or by members of the regulatory authorities, a joint session between these individuals and DSMC members (called an Open Session) may be held after the Closed Session. This session gives the DSMC an opportunity to query these individuals about issues that have arisen during their review in the initial Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved.
15. Open and Closed Tabulated Data Report

The Project Manager with the study statistician will prepare open tabulated data report for each DSMC meeting. The open tabulated data report will be available to the DSMC members and management committee and will include:

- One-page outline of the study design
- DSMC monitoring plan
- Major protocol amendments
- Study recruitment by month and by institution
- Baseline characteristics (blinded)
- Eligibility/protocol violations
- Completeness of follow-up
- Protocol compliance

The study statistician will prepare a closed tabulated data report in addition to the open tabulated data report for each DSMC meeting. The closed tabulated data report will be available to DSMC members only and will include:

- Analyses of primary and secondary efficacy endpoints
- Subgroup analyses
  - Age >45 years
  - Surgical/non surgical
- Analyses of adverse events and overall safety data
- Information on cross-over patients

16. Minutes of the DSMC Meeting

The DSMC will prepare minutes of their meeting. Two sets will be prepared: the Open Minutes and the Closed Minutes.

The Open Minutes will describe the proceedings in the Open Session of the DSMC meeting, and will summarise the recommendations by the DSMC. Since these minutes will be circulated immediately to the lead study investigators, it is necessary that these minutes do not unblind study processes.

The Closed Minutes will describe the proceedings from the entire DSMC meeting, including the listing of recommendations by the Committee. As these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DSMC. Copies will be archived by the DSMC Chair/Statistician, for distribution to the lead investigators, and regulatory authorities at the time of study closure.
17. Recommendations to the Management Committee

At the meeting of the DSMC during the conduct of the trial, the DSMC will make a recommendation to the Management Committee to continue or to terminate the trial. This recommendation will be based on safety considerations and will be guided by statistical monitoring guidelines defined in this Charter.

The MC is jointly responsible with the DSMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or pertaining to the conduct of the study, made by the DSMC, will be considered by the MC.

The DSMC will be notified of all changes to the protocol or to study conduct. The DSMC concurrence will be sought on all substantive recommendations or changes to the protocol or study conduct prior to their implementation.