The CLIP-II Study
Data Safety Monitoring Committee Charter

Title of the protocol:	A phase III multicentre blinded randomised controlled clinical non-inferiority trial of cryopreserved platelets vs. conventional liquid-stored platelets for the management of surgical bleeding The Cryopreserved vs. Liquid *Platelets trial: CLIP-II*

Protocol Number:	ANZIC-RC/MR002
Clinical Trial Registration	ClinicalTrials.gov NCT03991481 (CLIP-II) ACTRN12621000271808 (CLIPNZ-II)
Coordinating centre:	The Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University Level 3, 553 St. Kilda Rd Melbourne, Victoria 3004 Australia
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1. Introduction

This Charter is for the Data and Safety Monitoring Committee (DSMC) of the Cryopreserved vs. Liquid Platelet - II trials (CLIP-II) in Australia and New Zealand.

The purpose of this document is to describe the roles and responsibilities of the independent DSMC, the DSMC membership, its relationship with the trial's other committees, and the purpose, format and timing of its meetings. The Charter will also detail 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 Open and Closed Reports that will be provided to the DSMC.

This DSMC charter conforms with the National Health and Medical Research Council's Guidance on Data Safety Monitoring Boards 2018.

2. Primary Role and Responsibilities of the DSMC

The DSMC is a separate entity from the CLIP-II management committees (MC) and its members are fully independent of the sponsoring institution and all trial investigators. The independence of the DSMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from any adverse impact resulting from access to trial information.

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMC functions to provide expert and independent advice to the committee, so that jointly this can be assured.

The DSMC will review trial progress and accruing data of the trials at the scheduled interim analysis point and at any other time the DSMC deems necessary. This includes accumulated trial data on recruitment, data quality, protocol compliance and main outcomes and safety data.

Based on this review, the DSMC may make recommendations to the CLIP-II management committees. As a primary responsibility, the DSMC will consider and make an assessment of treatment safety. The DSMC may make recommendations to the CLIP-II Management Committees regarding the continuation without modifications, continuation with modifications, or termination of the study based on their review of scientific, medical, and ethical criteria. At their discretion, the DSMC may also formulate recommendations relating to the protocol or protocol changes such as the selection, recruitment, and retention of participants, their management, improving adherence to protocol-specified regimens and the procedures for data management and quality control.

The CLIP-II Management Committees will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue, modify or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

The DSMC serves in an advisory role to the CLIP-II Management Committees in regards to protocol amendments. Thus, the DSMC will be consulted regarding protocol changes but will not be responsible for providing formal approval of protocol changes. If the DSMC raises any concerns related to the study protocol or any proposed changes the CLIP-II management committees will consider and discuss these and an outcome will be reached by mutual agreement between the DSMC and the management committees.

The DSMC will review external information that may have an impact on the study. It will be the responsibility of the CLIP-II management committees to inform the DSMC of the results of related trials that conclude during the course of the CLIP-II trial or other information that arises that may impact on the study.

In line with standard research practice in Australia, there is no formal reporting by the DSMC to the National Health and Medical Research Council (NHMRC).

3. Membership of the DSMC

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

- Intensive care medicine and research
- Biostatistics
- Conduct, analysis and monitoring of randomised controlled trials
- Previous experience on DSMC.

DSMC Chair:	**Professor Duncan Young** Professor of Intensive Care Medicine University of Oxford Kadoorie Centre for Critical Care Research and Education John Radcliffe Hospital Oxford, UK
DSMC Members:	**Professor Simon Stanworth** Consultant haematologist National health Service Blood & Transplant/ Oxford University

	Hospitals NHS Foundation Trust Radcliffe Department of Medicine University of Oxford Oxford, UK
	Associate Professor Jeffrey Presneill Deputy Director of Intensive Care Medicine Head of Quality and Care Department of Intensive Care Medicine The Royal Melbourne Hospital Melbourne, Australia
Independent Trial Statistician	**Professor Michael Bailey** Principal statistical consultant, School of Public Health & preventive Medicine, Monash university, Melbourne, Australia

4. Conflicts of Interest

The DSMC membership has been restricted to individuals free of any competing interest that may impact on the trial. The nature of a competing interest may be financial, scientific or regulatory in nature. Any competing interest or lack thereof, which may be real or potential should be declared in writing.

Any DSMC member who develops potentially relevant conflicts of interest during the course of the trial should promptly bring these to the attention of the DSMC chairperson for a decision by the remaining committee members as to the individual's ongoing eligibility to function within the committee. The DSMC will be responsible for deciding whether these competing interests materially impact objectivity.

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 DSMC will promptly appoint their replacements.

5. Timing and Purpose of the DSMC Meetings and Reports

5.1 Initial Organisational Meeting

The initial meeting of the DSMC will be an Organisational Meeting which is held before the start of the trial. This Organisational Meeting will be attended by the DSMC chair, the trial Chief Investigator, project manager and the trial statistician.

The meeting will provide opportunity for advisory review of scientific and ethical issues relating to study design and conduct, discuss the standard operating procedures for the role and functioning of the DSMC, and 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 current copies of the clinical trial protocol, the DSMC Charter, and the current versions of the case report forms and SAE forms.

This meeting may occur via teleconference or through email exchange.

5.2 Interim Analysis

One interim analysis is planned for each of the CLIP-II and CLIPNZ-II studies. This will be performed after recruitment of 50% of the target number of patients transfused trial platelets has reached 90 day outcome. A cut-off date one month after the last of the these patients reaches their 90 day follow up will be set so the interim analysis is conducted in a timely manner.

The independent trial statistician will prepare the data for the DSMC for discussion at a formal closed meeting. Data prepared for the interim analysis should be available to the DSMC members in advance of the meeting. Data will be analysed with treatment group indicated by a binary code, without revealing which is control or intervention. Un-blinding of these data will occur only if requested by the DSMC. All coded and unblinded data will remain confidential to the DSMC and the independent trial statistician.

A teleconference attended by all members of the DSMC and the trial statistician, will be organised as soon as possible after the 90-day follow up censor period of one month and data are analysed. A consensus decision of the DSMC will be required to make a recommendation regarding early cessation of the trial. In the event a consensus decision cannot be reached, subsequent interim analyses may be undertaken prior to further consideration of early cessation.

5.3 Additional Data Reporting

The DSMC can request any additional data at other intervals at their discretion.

6. Adverse Event (AE) reporting

Adverse events (AEs) are defined as any untoward medical occurrence in a participant or clinical investigation subject administered the study interventional intervention and which does not necessarily have to have a causal relationship with the study treatment.

In the intraoperative and immediate postoperative period, cardiac surgical patients will experience many aberrations in laboratory values, and many abnormal signs and symptoms, due to the nature of the underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they are considered to be,

in the judgement of the site principal investigator, related to transfusion of study platelets.

AEs will be reported upon for the duration of the hospital admission.

All suspected attributable AEs are to be reported to the site Principal Investigator as soon as there is knowledge of the event. The site Principal Investigator will be responsible for determining the causal relationship as either not related, unlikely, possibly, probably or definitely study treatment related. AEs decided to be possibly, probably or definitely causally related to study platelets will be reported to the coordinating centre staff and recorded in a safety database that will be available to the DSMC on request. Non-serious adverse events will not be individually notified to the DSMC, site HRECs or the Australian Therapeutic Goods Administration or Medsafe New Zealand in accordance with local practice. However, the DSMC will have free access to the safety database at all times upon request and will make recommendations for the ongoing conduct of the trial based on this information.

7. Serious Adverse Event (SAE) reporting

Serious Adverse Events (SAEs) are defined as any untoward medical occurrence that meets one or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity, or disability/incapacity that is likely to become persistent or significant;
- Is a congenital anomaly/birth defect; or
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

Given that perioperative high risk cardiac surgical patients might experience any of the above listed criteria in the course of their ICU admission, regardless of involvement in the trial, only SAEs that are reasonably suspected by the site principal investigator to be possibly, probably or definitely causally related to the study treatment will be reported.

SAEs will be reported upon for the duration of the hospital admission.

SAEs should be reported to the coordinating centre, by entering into the study website, within 24 hours of study staff becoming aware of the event.

The Coordinating Centre will report each SAE to the chair of the DSMC as soon as possible after receiving notification, who will make recommendations as appropriate.

8. Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting

An SAE whose nature, severity, specificity, or outcome is not consistent with the expected complications of the intervention described in the investigator brochure will be considered "unexpected". SUSARs will also be reported to the coordinating centre by entering required data into the study website within 24 hours of participating site study staff becoming aware of the occurrence.

The Coordinating Centre will report each SUSAR to the DSMC, which will make recommendations as appropriate.

9. 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 trial. An exception will be made to permit access to the independent trial statistician who will be responsible for serving as a liaison between the database and the DSMC. The study's project manager will have immediate access on an ongoing basis to patient-specific information on 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 CLIP-II Management Committees. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy and safety results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues.

Any recommendations made by the DSMC will be formally communicated to the Chief Investigators and the project managers in writing.

10. Closed Sessions

For the reviews referred to in sections 5.2 and, as required, 5.3, a closed session involving only DSMC membership and the trial statistician, will be held to allow discussion of confidential data from the clinical trial, including information about the safety of interventions. This will allow the independent trial statistician to guide the DSMC members through the data.

The independent trial statistician will facilitate the discussion by explaining the analysis and responding to any statistical queries pertaining to the interim analysis. The members will then have time to discuss the confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. To ensure

that the DSMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMC will receive data analysed with treatment group indicated by a binary code, without revealing which is control or intervention. Un-blinding of these data will occur only if requested by the DSMC.

At 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 without modifications, continue with modifications, or stop.

11. Open Session

In order to allow the DSMC to have adequate opportunity to discuss the study generally, a joint session between DSMC members, the trial statistician and each CLIP-II chief investigator and project manager (called an Open Session) will be held. This will occur before the Closed Session of the interim analysis. A further open session can occur after the closed session, at the discretion of the DSMC.

Open sessions are not mandated at any additional sessions of the DSMC to review data reports, unless requested by the DSMC. Open session/s give the DSMC an opportunity to query these individuals about issues that have arisen during their review in the Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved.

12. Open and Closed Reports

For each DSMC meeting, Open and Closed reports will be provided.

Open Reports, available to all who attend the DSMC meeting, will include data:

- on screening & recruitment
- pooled data on eligibility/protocol violations
- completeness of data & follow-up and
- compliance
- data management, monitoring & quality

The Open Reports will be prepared by the project manager.

Closed Reports, available only to those attending the Closed Sessions of the DSMC meeting, will include:

- analyses of primary and secondary efficacy endpoints,
- analyses of AEs, SAEs and safety endpoints,

The Closed Reports will be prepared by the independent trial statistician.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within one month of the date of the DSMC meeting. The Reports should be provided to DSMC members at least one week prior to the date of the meeting.

13. Minutes of the DSMC Meeting

Two sets of minutes will be prepared from the meeting: the Open Minutes and the Closed Minutes. The open minutes will be prepared by the trial project manager. The DSMC will keep minutes of their closed session of the meeting. As it is likely that these minutes could contain coded or unblinded information, it is important that they are not made available to anyone outside the DSMC. Rather, copies will be archived by the DSMC Chair, for distribution to the lead investigators, and regulatory authorities at the time of study closure, if requested.

14. Recommendations to the Management Committee (MC)

At each meeting of the DSMC during the conduct of the trial, the DSMC will make a recommendation to the each CLIP-II trial management committee. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this Charter. Possible recommendations for the DSMC include:

- Trial to continue as planned
- Trial to continue with modification/s
- Early stopping due to safety. There is no intention to stop at the interim analysis for futility as this is a non-inferiority trial.
- Proposing or commenting on proposed changes to protocol

Each CLIP-II trial Management Committee is jointly responsible with the DSMC for safeguarding the interests of participating patients and for the conduct of the trial. Each CLIP-II trial Management Committee will be ultimately responsible for deciding whether to continue, modify or to stop the trial based on the DSMC recommendations. Each CLIP-II management committee will communicate to site investigators and applicable ethics committees the DSMC recommendations.

The DSMC will be notified of all protocol amendments as detailed in section 2.

15. Statistical Monitoring Guidelines

Stopping rules will be based on a responsibility to inform the investigators if the randomised comparisons provide evidence beyond reasonable doubt of a difference between randomised groups in major measures of safety or effectiveness.

DSMC Member	**Signature**	**Date**

Prof Duncan Young		
Prof Simon Stanworth		
A/Prof Jeffrey Presneill		

The DSMC member signature on this charter indicates approval of the content and agreement to adhere to the charter.