RECOMMEND Platform Trial:
CORE PROTOCOL

Generating new evidence to REduce major COMplications to iMprove the safety and efficacy of Extracorporeal membrane oxygenatioN (ECMO) in severe carDiac and respiratory failure Platform Trial

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Contact information:
The Australian & New Zealand Intensive Care Research Centre
Department of Epidemiology and Preventive Medicine
School of Public Health and Preventive Medicine
Monash University
Level 3, 553 St Kilda Road, Melbourne
Victoria 3004, AUSTRALIA
Phone: +61 3 9903 0247
Email: anzicrc@monash.edu

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1. SYNOPSIS

Title	RECOMMEND Platform Trial Core Protocol
Background	Patients in the intensive care unit (ICU) undergoing extracorporeal membrane oxygenation (ECMO) require close monitoring and interventions to support their recovery. The RECOMMEND Platform Trial aims to develop clear, high-quality evidence for ECMO care, to better inform clinicians in this rapidly evolving field. The RECOMMEND Platform Trial will provide a 'platform' for funding, logistics, and training protocols. This approach enhances efficiency, allowing research to begin and complete more efficiently. The platform maintains rigorous standards and provides a safe, cost-effective and time-efficient method for generating knowledge about ECMO care. The RECOMMEND Platform Trial is embedded in the Australian and New Zealand bi-national EXCEL Registry. The EXCEL Registry is an existing multidisciplinary network of integrate care for critically ill patients requiring ECMO. The EXCEL registry provides data to registry-embedded clinical trials, and aims to monitor long term outcomes for ECMO patients and identify best clinical practice. Overall, platform trials offer a dynamic and innovative approach that enables the simultaneous evaluation of multiple treatments and the rapid translation of scientific discoveries into improved patient care. The RECOMMEND Platform Trial has been informed by patient preferences and values through our consumer engagement. RECOMMEND will evaluate the safety and effectiveness of various interventions in one or more domain. This approach supports continuous learning and real-time clinical decision-making to improve patient outcomes.
Aim	The aim of the **RECOMMEND Platform Trial** is to determine, in patients with acute cardiorespiratory failure requiring ECMO, the efficacy, safety and cost-effectiveness of various interventions.
Objectives	**Primary Objective** To determine the effect of a range of interventions on survival, organ support and resource utilisation to day 28 for hospitalised patients receiving ECMO. **Secondary objectives** To determine (at day 28): major complications (major haemorrhage and intracranial haemorrhage); ECMO and ventilator free days; and mortality.
Study Design	The RECOMMEND Platform Trial is a registry-embedded (EXCEL Registry), randomised, platform trial comparing interventions for patients receiving ECMO.
Sample Size and Statistical Considerations	There is no set sample size as this is an adaptive platform trial. Bayesian statistical methods will be used to perform the interim analyses and final analyses, using pre-defined Statistical Triggers thresholds for decision making within a domain.

Eligibility Criteria	**Inclusion Criteria** • Patients receiving ECMO • Patients enrolled in the EXCEL Registry **Exclusion Criteria** • Treating clinician regards death as imminent and inevitable • Treating clinician determines it is not in the patient's best interests • Patient previously enrolled in the RECOMMEND Platform Trial in the last 28 days
Outcomes	***Primary Outcome*** The Daily Organ Support for patients on ECMO (DOSE-score), a 6-level daily ordinal outcome measured as the worst status of a patient on each day from day 1 to day 28 inclusive. The DOSE score reflects survival, organ support, resource utilisation and discharge status where the 6 levels are: 1) dead; 2) on ECMO; 3) invasively mechanically ventilated without ECMO; 4) in ICU but not invasively mechanically ventilated nor on ECMO; 5) in hospital; and 6) discharged from the hospital alive. ***Secondary Outcomes Measured at Day 28*** • Development of major haemorrhage • Development of intracranial haemorrhage • Mortality • ECMO-free days • Ventilator-free days
Study Duration	The RECOMMEND Platform Trial is designed to be ongoing and may accept new domains as they become relevant, continuing whilst any active domains have objectives to complete.
Clinical Trial Registration	ClinicalTrials.Gov: NCT06526533

2. ABBREVIATIONS & KEY DEFINITIONS

2.1. Abbreviations

ADR	Adaptive Design Report
AE	Adverse Event
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
CRF	Case Report Form
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
DSA	Domain-Specific Appendix
DSMC	Data Safety and Monitoring Committee
DMC	Data Management Centre
DSSAP	Domain Specific Statistical Analysis Plan
DSWG	Domain-Specific Working Group
ECMO	Extracorporeal Membrane Oxygenation
EXCEL	Bi-national registry of integrated care for critically ill patients on ECMO
eCPR	Extracorporeal cardiopulmonary resuscitation
GCP	Good Clinical Practice
HEAP	Health Economics Analysis Plan
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
ITT	Intention to Treat
LAR	Legally Authorised Representative
LOS	Length of Stay
MC	Management Committee
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
RC	Research Coordinator
RECOMMEND	Generating new evidence to **RE**duce major **COM**plications to i**M**prove the safety and efficacy of **E**xtracorporeal membrane oxygenatio**N** (ECMO) in severe car**D**iac and respiratory failure
RSI	Reference Safety Information
SAC	Statistical Adaptation Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDT	Statistical Design Team
SUSAR	Suspected Unsuspected Serious Adverse Reaction

QALY	Quality Adjusted Life Year
VA ECMO	Venoarterial Extracorporeal Membrane Oxygenation
VV ECMO	Venovenous Extracorporeal Membrane Oxygenation
WHODAS	World Health Organization Disability Assessment Schedule

2.2. Key Definitions

Borrowing is the process within the statistical model, whereby, when the treatment effect is similar in different patient groups, evidence relating to the effectiveness of an intervention in one group contributes to the estimation of the treatment effect in another group. Within the RECOMMEND Platform Trial this will be achieved using Bayesian hierarchical models.

Core Protocol is a module of the protocol documents that governs the trial and contains all information that is generic to the platform trial, irrespective of the domains or interventions that are being tested.

Domain consists of a specific set of interventions within a common clinical mode that are mutually exclusive for the purposes of the platform. Where there is only a single intervention option within a domain, the comparator is all other usual care in the absence of the intervention. Where multiple interventions exist within a domain, comparators include the range of interventions, which may include a no-intervention option. Within the RECOMMEND Platform Trial every participant will be assigned to receive one and only one of the available interventions within each eligible domain.

Domain-Specific Appendices (DSA) are appendices to the Core Protocol. These appendices are modules that contain information relevant to a specific group of interventions which are nested within a domain. Each domain will have its own DSA which includes specific eligibility criteria for patients, features of the interventions and how they are delivered, and any additional endpoints and data collection not covered in the Core Protocol.

Domain-Specific Working Group (DSWG) is a sub-committee involved in Domain management, the members of which take responsibility for the development and management of a current or proposed domain.

Intervention is a treatment option that is subject to variation and is being subjected to manipulation for the purpose of comparison within the design of a domain. An intervention within a Domain may be a "no treatment" option, usually referring to continuation of standard care.

Platform Conclusion describes a decision of the Management Committee (MC) to conclude that superiority, inferiority or futility has been demonstrated following the occurrence of a statistical trigger that has been evaluated by the DSMC. Under most circumstances a Platform Conclusion leads to a Public Disclosure of the result via presentations and publications, and may result in interventions being removed from the platform or closure of a domain.

Platform Trial is a type of clinical trial that can study multiple interventions simultaneously allowing for the evaluation of multiple research questions simultaneously. Platform trials may be perpetual with substitution of answered research questions with new questions as the trial evolves.

Public Disclosure is the communication of a Platform Conclusion to the broad medical community by means of presentation, publication or both.

Regimen describes the combination of interventions, including controls, across one or more domains that a participant has been allocated in a multifactorial platform trial, with one intervention allocated per domain. ***Statistical Adaptation Committee (SAC)*** takes responsibility for running predetermined statistical models at each interim analysis. This committee usually consists of independent statisticians sub-contracted by the coordinating centre to undertakes statistical analysis.

Statistical Model is a computational algorithm that is used to estimate the posterior probability of superiority, inferiority or futility of the regimens and/or interventions being evaluated for a trial domain.

Statistical Trigger occurs when a threshold has been crossed for a particular decision rule. Statistical triggers may involve decisions regarding superiority, inferiority and futility of the interventions under investigation within the platform. A Statistical Trigger applies to the smallest unit-of-analysis specified for a given domain, but may be reached in more than one unit-of-analysis for the same intervention at the same adaptive analysis (e.g. in different strata).

Stratum / Strata (plural) a set of mutually exclusive and exhaustive categories (stratum), defined by baseline characteristics of a patient within the trial, in which the relative effects of interventions may differ. These potentially differential effects are reflected in the statistical model and the Platform Conclusions. The criteria that define a stratum must be present at or before the time of enrolment.

Unit-of-analysis is the group of patients analysed together within the model for a particular domain. The unit-of-analysis can be all patients who have received an allocation status in that domain or a sub-group of patients whose allocation status is determined by their status with respect to one or more strata.

3. ADMINISTRATION STRUCTURE

3.1. Trial Sponsor/Coordinating Centre

The study sponsor is Monash University, acting through the coordinating centre: **The Australian & New Zealand Intensive Care Research Centre (ANZIC-RC).** Both Monash University and the ANZIC-RC, as represented by key investigators and support staff on the MC, will be involved with all aspects of the trial development, activation, recruitment, data collection and analysis, and the dissemination of results.

The Australian & New Zealand Intensive Care Research Centre
School of Public Health and Preventive Medicine
Monash University
Level 3, 553 St Kilda Road, Melbourne
Victoria 3004, AUSTRALIA
Phone: +61 3 9903 0247
Fax: +61 3 9903 0071
Email: anzicrc@monash.edu

3.1.1. Sponsor/Co-ordinating Centre Responsibilities

Responsible for all aspects of study management including:

- Management of study budget and liaison with funding bodies
- Final protocol
- Case Report Form design
- Database development, maintenance and administration
- Data management
- Protocol training of PIs and RCs
- Protocol training of site pharmacists
- Preparation and arrangement of investigator payments
- Management of regulatory affairs (TGA etc.)
- Management of study set up including assistance with HREC applications
- Study website
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Liaison with independent DSMC
- Data analysis and collaboration on publications

3.1.2. Key Coordinating Centre Staff

Staff Name	**Role**
Prof. Carol Hodgson	*Deputy Director ANZIC-RC* *Chief Investigator RECOMMEND Platform Trial*
Mr. Tony Trapani	*Research Manager ANZIC-RC*
Ms. Victoria King	*Business manager ANZIC-RC*
Curtis Hopkins	*Project Manager RECOMMEND Platform Trial*

3.2. Management Committee

The MC are responsible for executive decision-making that considers the interests of the trial, participants, and funders/sponsors.

3.2.1. Management Committee Responsibilities:

- Oversight and strategic direction of the RECOMMEND Platform Trial and Domains
- Development of protocol, investigator brochure, participant information brochures, case report form (CRF), patient information and consent form, and other core trial documents
- Approval of DSAs developed or amended by each DSWG
- Identification and approval of participating sites
- Submission of protocol, investigator brochure, participant information brochures, and patient information and consent form for ethical approval
- Oversight of data analysis and final approval of data for analyses
- Liaise with the DSMC for data safety and monitoring and Platform conclusions
- Obtaining and oversight of study budget
- In conjunction with DSWGs, the analysis and reporting of study domains
- Approval of manuscripts reporting results that are submitted by DSWGs

3.2.2. Management Committee Members:

Member Name
Prof. Carol Hodgson (Chair)
Prof. David J. (Jamie) Cooper
Prof. Zoe McQuilten
Prof. John Fraser
Prof. Eddy Fan
Prof. Stephane Heritier
Prof Vincent Pellegrino
Assoc. Prof. Neil Orford
Assoc. Prof. Priya Nair
Assoc. Prof. Aidan Burrell
Dr. Ary Serpa Neto
Dr. Elizabeth Ryan
Dr. Alisa Higgins
Dr. Nicole Ng
Mr. Curtis Hopkins
Mr. Bentley Fulcher
Mr Craig Dicker
Ms Shannah Anderson

3.3. Domain Specific Working Group

Each active and future Domain will be administered by a Domain Specific Working Group (DSWG), which will serve as subject matter experts for that domain under the oversight of the MC.

The DSWG will evaluate potential aims for their domain and prioritise their importance based on newly emerging preclinical and clinical data. They will work with the RECOMMEND Platform Trial MC to report results from the domain.

Responsibilities of each DSWG include:

- Development and of the DSA
- Development and execution of amendments to the DSA
- Proposal and development of new interventions within the domain

- Development of a domain-specific statistical analysis plan (DSSAP) for reporting results upon meeting a platform conclusion
- Obtaining funding to support the domain, with a requirement that any funds obtained contribute appropriately to the overall conduct of RECOMMEND Platform Trial

Membership of each DSWG is set out in the corresponding DSA and should comprise subject matter experts providing broad representation, content knowledge of the domain, and expertise in trial conduct and design.

3.4. Data Management Centre

The Data Management Centre (DMC) is responsible for the following:

- Ensuring the completeness and accuracy of data collected required by the DSMC and MC.
- Performing timely validation of data, queries and corrections.
- Providing database extracts as specified by the Statistical Teams (described below). The database extracts will be used to generate full DSMC reports, to create the analysis datasets the SAC will use to perform the adaptive analyses, and to create the analysis datasets for final analyses (after a platform conclusion has been reached).
- Assist in CRF development and liaise with sub-contracted database providers

3.5. Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will be appointed. The DSMC will consist of experts appointed to monitor the safety and scientific integrity of the RECOMMEND Platform Trial and its domains. Prior to participant recruitment in the RECOMMEND Platform Trial, a DSMC charter will be agreed upon between the RECOMMEND Platform Trial MC and the DSMC.

3.6. Statistical Design Team

The Statistical design team (SDT) will be responsible for developing the Statistical Analysis Plan (SAP) for the RECOMMEND Platform Trial, as well as determining pre-specified stopping rules and statistical adaptations to be applied to the trial. The SDT will adhere to the DSMC charter and will be blinded to aggregate data. The SDT may also perform analyses for domains or interventions that have been unblinded (e.g., once a platform conclusion has occurred for a domain), whilst remaining blinded to information about other interventions and domains that are still recruiting.

3.7. Statistical Adaptation Committee

An independent SAC will be established to implement the adaptive analyses according to the pre-specified design using unblinded endpoints data in the trial and will determine if any of the pre-specified statistical triggers have been met. The SAC:

- Will conduct all unblinded analyses
- Report statistical conclusions to the DSMC
- Will be unblinded to aggregate data

3.8. Independent Statistical Team

An independent, unblinded statistical team (based at the coordinating centre) will be established to perform the analyses required to produce the periodic safety and efficacy reports to the DSMC (Open and Closed Reports). They will receive database extracts from the Data

Management Centre (to prepare the full safety and efficacy DSMC reports) and will also prepare/format the data required by the SAC for the adaptive analyses. This team is separate to the SAC, and will be a point of contact for the SAC and facilitate data transfer (where needed). They may also be involved in running some of the analyses that are performed once a domain has reached a platform conclusion, to prevent unblinding of information to the blinded SDT for ongoing interventions or domains.

3.9. Health Economics Working Group

The Health Economic Working Group will be established to conduct health economic evaluations alongside the platform and therapeutic domains. The Group will conduct blinded cost-effectiveness analyses alongside domains following a statistical trigger. A detailed description of how the health economic analyses will be conducted for reporting the cost-effectiveness of interventions will be presented in the Health Economics Appendix to the Master Protocol and the Domain-specific Health Economic Analysis Plans (HEAPs) as appropriate. The Health Economic Working Group will also coordinate with the MC and DSWG by providing health economic expertise on protocol documents, domains, and sub studies.

3.10. Consumers

The RECOMMEND Platform Trial has two critical care survivors with lived experience of ECMO on its MC. Our two consumers have been Associate Investigators for the RECOMMEND Platform Trial since its inception. They have actively contributed to grant applications as well as development of this protocol, DSAs and outcome measures. We will continue to work closely with our consumers as we develop future domains for the platform trial. Our consumers will continue to provide feedback on trial design through ongoing consultation and involvement with the MC.

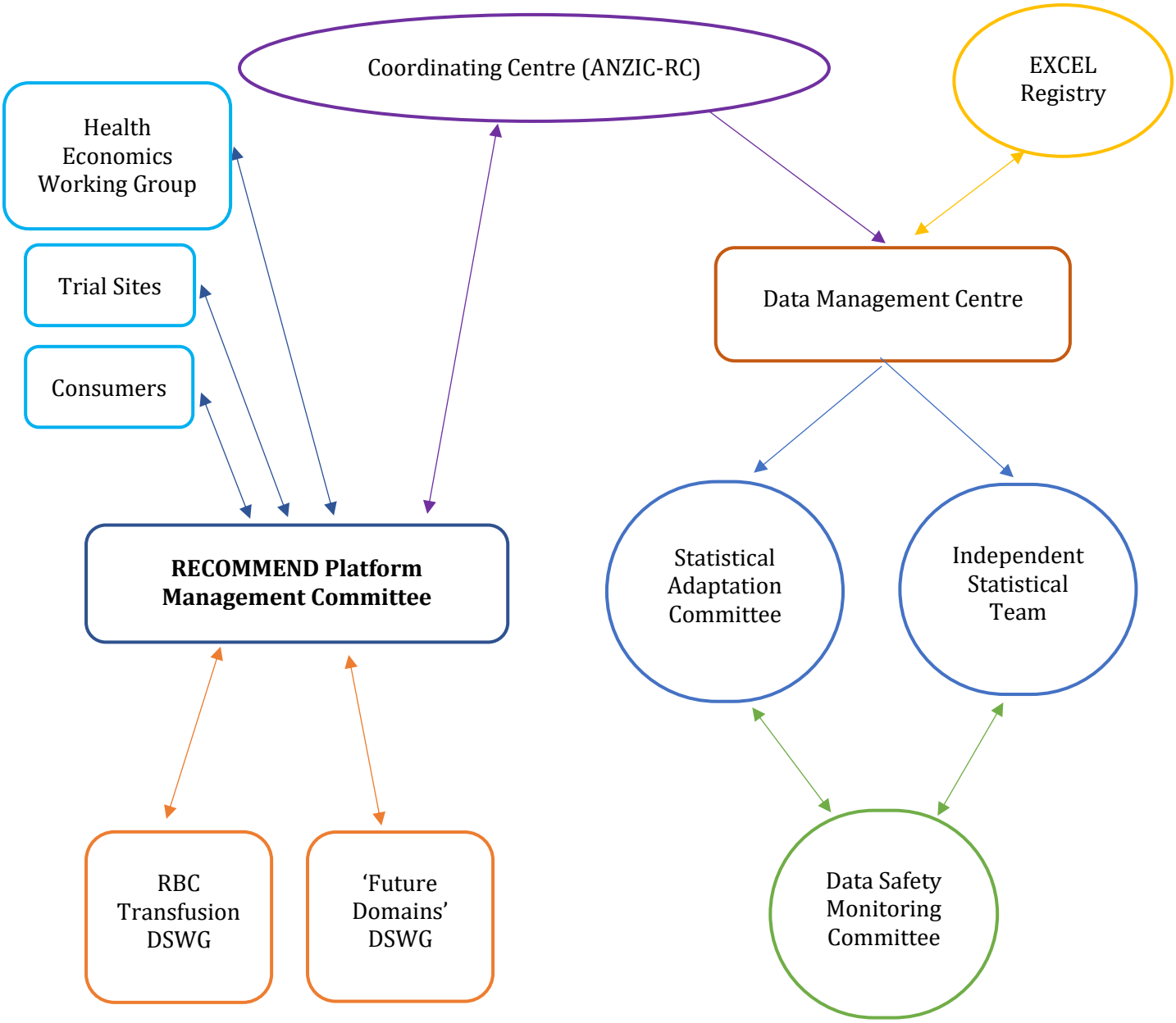
3.11. EXCEL Registry

The RECOMMEND Platform Trial is embedded within the EXCEL Registry (HREC/43134/Alfred/534/18), a binational ECMO registry with an established network of over 30 Australian & New Zealand Intensive Care Units (ICUs). The EXCEL Registry provides established infrastructure and a high-quality, detailed, prospective registry of ECMO data.

Data used in the RECOMMEND Platform Trial will include:

- Data obtained through a RECOMMEND Platform Trial CRF
- Data obtained from the EXCEL Registry
  Any additional data obtained through a domain-specific CRF (as outlined in the DSAs)

3.11.1. Figure 1: RECOMMEND Organisation Chart

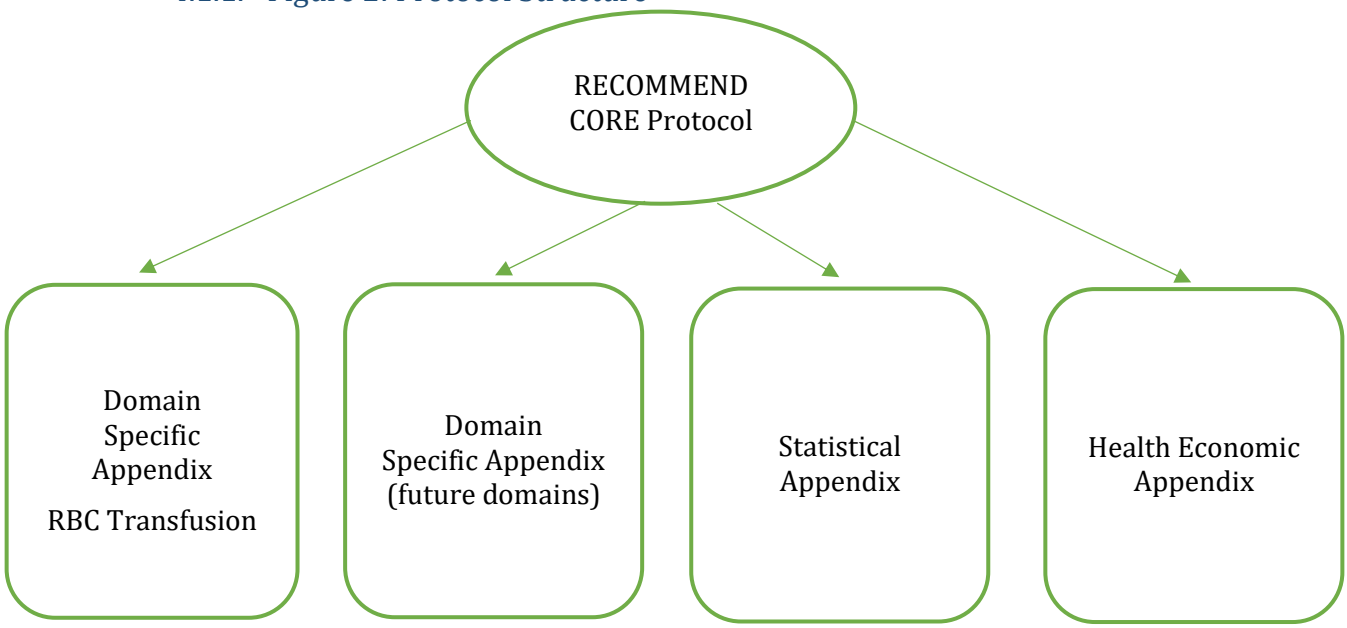


4. PLATFORM TRIAL PROTOCOL STRUCTURE

4.1. Overview

The structure of this protocol is different to that of conventional clinical trials. It is designed to allow the trial to evolve over time by introducing new domains, interventions, or both (see glossary for definitions). The basic structure of the protocol is outlined in Figure 1.

4.1.1. Figure 2: Protocol Structure



The structure of the protocol includes:

- Core Protocol
- Domain Specific Appendices
- Statistical Appendix
- Health Economic Appendix

4.2. Core Protocol

This document is the Core Protocol and contains all information relevant to the trial's overarching processes for the duration of the trial. The Core protocol includes:

- The background and rationale for study management and outcomes related to ECMO care.
- Rationale for the use of a Bayesian adaptive platform trial structure.
- Trial governance and operational structures.
- Data management processes.

4.3. Domain-Specific Appendix (DSA)

DSAs should be read in conjunction with the Core Protocol. Each Domain may have specific eligibility criteria, data points and secondary and tertiary outcome measures. Sites may not wish to participate in all active domains at any point in time. Site participation in domains is dependent on workload, patient availability, workforce pressures and equipoise. DSAs will contain the following information for sites recruiting to that domain:

- Background and rationale

- Additional eligibility criteria
- Description of the interventions and procedures for their delivery
- Data collection and endpoints
- Ethical considerations
- Consent models and procedures
- Organisational considerations
- Statistical components
- Health economic components

5. BACKGROUND & RATIONALE

5.1. The Need for Improved ECMO Care Recommendations

Extracorporeal Membrane Oxygenation (ECMO) is an invasive and resource intensive treatment used to support critically ill patients suffering from severe cardiac arrest, cardiac failure or respiratory failure.[1,2] ECMO provides mechanical circulatory support, temporarily replacing the function of the heart and/or lungs, allowing time for these organs to recover.[3]

Globally, the use of ECMO has increased rapidly over the past decade. It is both invasive and expensive, with the average cost for a single admission in Australia exceeding more than $180,000 and a total annual cost of > $75 million.[4] Despite its high cost, ECMO is associated with a high mortality rate, and many survivors have compromised functional recovery for months or years after discharge from hospital, further adding to the long-term costs of care.[5,6]

The main complications reported in the national ECMO registry from 2019-2022 include bleeding (51.4%), renal failure and fluid overload (78.4%), and death and ongoing disability (66%). These were confirmed as research priorities by consumers[2] and end-users.[7] While the use of ECMO increases swiftly, the evidence base to support the growing patient numbers receiving this care has not grown at the same rate, resulting in important evidence gaps.[8,9]

The RECOMMEND Platform Trial will address these evidence gaps in ECMO services in Australia. A platform trial is a type of study design that evaluates multiple interventions for a single condition or multiple interventions simultaneously within a single, overarching framework. This framework operates similarly to a standard operating procedure for study logistics, ethics management, funding, staffing, and statistical and data collection methods.[10] Having an approved process (platform) for the 'Platform Trial' to operate under potentially saves time and money and increases speed of clinical trial onboarding to outcome resolution for researchers, hospital staff, ethics committees, and stakeholders. With this platform in place, future studies of interventions for patients on ECMO can be onboarded more efficiently, as described above, and it creates a more powerful pool of data for impactful patient-centred research.

5.2. Principles of Platform Trials

There are several key ways in which the Platform Trial methodology provides value:

Flexible and Adaptive Design: Unlike traditional clinical trials that test a single treatment for one condition, a platform trial allows for flexibility and adaptability. This approach allows for different treatments to be added or removed over time as new information becomes available, but only at the discretion of the Human Research Ethics Committee (HREC) and MC.

Core Protocol: A platform trial operates under a single core protocol, which outlines the overall structure, objectives, and rules governing the trial. This protocol serves as a blueprint for

conducting the study and provides guidelines for adding or modifying treatment arms as the trial progresses.

Multiple Study Domains: Within a platform trial, there are multiple domains, each testing a set of different interventions. By testing multiple treatments across multiple domains simultaneously, researchers can efficiently compare their effectiveness and safety, saving significant time, cost, and other resources compared to running completely separately trials for each intervention.

Efficiency and Speed: By testing multiple treatments simultaneously and incorporating adaptive elements, platform trials can be more efficient and faster than traditional clinical trials. They allow for the rapid evaluation of multiple interventions, potentially accelerating the pace of medical research.

5.2.1. Adaptation of Domains and Interventions

Over the lifetime of RECOMMEND, it is anticipated that new interventions will be added as new domains. The creation of new domains will be considered according to priorities set by relevant working groups, based on existing or new clinical need and there being sufficient statistical power available within RECOMMEND. All new interventions and domains will require ethics and regulatory approval prior to being implemented at any site.

6. AIM

The aim of the **RECOMMEND Platform Trial** is to determine, in patients with acute cardiorespiratory failure requiring ECMO, the efficacy, safety and cost-effectiveness of a range of interventions.

7. OBJECTIVES

7.1. Primary Objective

The primary objective of this Platform is, for hospitalised patients receiving ECMO, to evaluate the effect of a range of interventions on survival, organ support and resource utilisation to day 28.

7.2. Secondary Objectives

To assess (at day 28): major complications (major haemorrhage, intracranial haemorrhage); at; ECMO and ventilator free days; and mortality.

8. STUDY DESIGN

8.1. Overview

The RECOMMEND Platform Trial design enables multiple treatment considerations and combinations within ECMO care to be evaluated in a simultaneous manner. The RECOMMEND Platform Trial allows interventions to be regularly evaluated to support continuous learning and real-time clinical decision-making. The Platform Trial allows for rapid implementation of treatments that may improve outcomes for this cohort of patients who are at high risk of death and disability.

8.2. Study Setting

The Platform will only recruit participants admitted to an ICU at a participating site. The study may be conducted in multiple regions as the number of domains grow.

Participating hospitals will be selected by the MC on the basis of criteria (including resources available to support research activities and track record in conducting investigator-initiated clinical trials)

There is no limit to the number of regions and number of participating sites.

8.3. Eligibility Criteria

All patients enrolled in the EXCEL Registry who meet the inclusion and none of the exclusion criteria.

8.3.1. Inclusion Criteria:

- Patients receiving ECMO
- Patients enrolled in the EXCEL Registry

8.3.2. Exclusion Criteria:

- Treating clinician regards death as imminent and inevitable
- Treating clinician determines it is not in the patient's best interests
- Patient previously enrolled in the RECOMMEND Platform Trial in the last 28 days

8.3.3. Domain-specific Entry Criteria

Participants who meet all of the core platform inclusion criteria and none of the core platform exclusion criteria can be considered for enrolment into one or more of the active RECOMMEND Platform Trial domains.

Enrolment into one or more RECOMMEND Platform Trial domains will be considered according to whether that domain has any additional inclusion or exclusion criteria, as outlined in each DSA, and if the participant meets those criteria.

Where a participant meets an exclusion criterion within a domain, but not another, the participant can be randomised to an intervention within the domain/s that the participant is eligible for (and is not randomised to an intervention in any ineligible domains).

8.4. Sample Size

Since this is an adaptive platform trial, there is no fixed sample size that determines when the study will end. This study uses a perpetual design where the sample size will grow with the addition of new interventions and domains. Frequent interim analyses will be performed so that questions can be concluded as soon as there is sufficient evidence. Simulations will be used to ensure that there is sufficient error control and power within each domain as it is added to the platform trial, and to inform the default and domain-specific thresholds for the statistical triggers. Individual domains may have fixed caps on their sample size as described within their DSAs.

8.5. Interventions

All information related to the background, rationale, and specification of interventions that will be administered within the trial, and applicable strata, are located in the DSAs. The minimum number of interventions within a domain is two and the maximum number is limited only by statistical power and operational feasibility.

8.6. Endpoints

8.6.1. Primary Outcome Measure

The primary outcome is the Daily Organ Support for patients on ECMO (DOSE-score), a 6-level daily ordinal outcome measured as the worst status of a patient on each day from day 1 through to day 28 inclusive, which reflects survival, organ support and resource utilisation:

1) dead;
2) on ECMO;
3) invasively mechanically ventilated without ECMO;
4) in ICU but not invasively mechanically ventilated nor on ECMO;
5) in hospital; and
6) discharged from the hospital alive.

8.6.2. Secondary Outcome Measures at Day 28

- Development of major haemorrhage
- Development of intracranial haemorrhage
- Mortality
- ECMO-free days
- Ventilator-free days

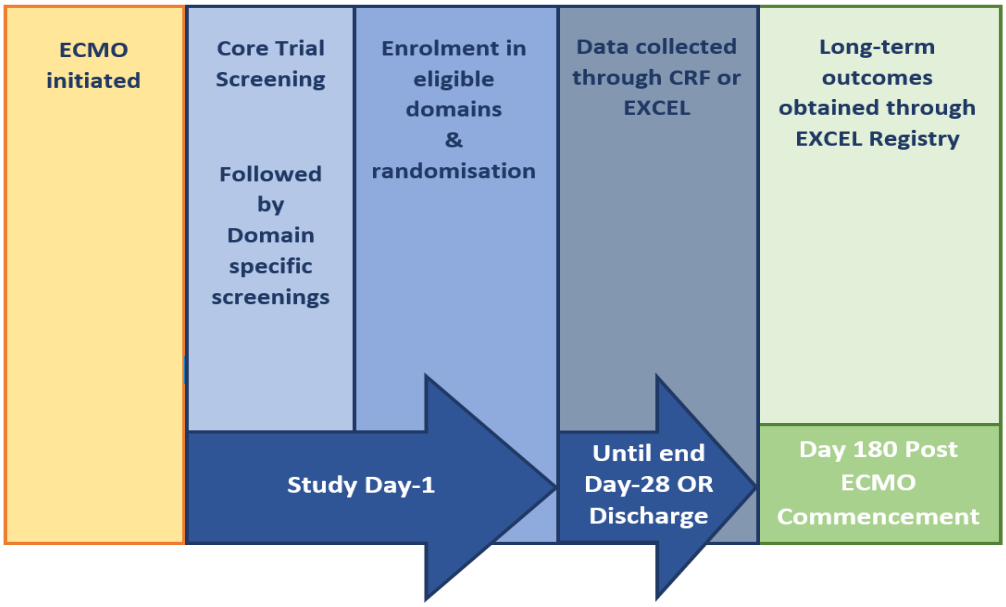
8.6.3. Tertiary Outcome Measures

Formal hypothesis testing will not be carried out on all tertiary outcomes.

- Mortality at 180 days
- Disability at 180 days
- Quality of life assessed at 180 days
- Functional status assessed at 180 days
- ICU length of stay
- Hospital length of stay (separated for survivors and non-survivors)

8.7. Participant timeline

8.7.1. Figure 3: Participant Timeline



8.8. Participating Sites

EXCEL Registry ECMO centres will be invited to participate.

8.9. Screening & Randomisation

8.9.1. Screening

All adults receiving ECMO at participating ECMO centres will be screened for eligibility. Each study centre will have experienced staff familiar with identifying and randomising patients in ICU.

8.9.2. Randomisation

The study will randomly allocate participants to one intervention within a domain. Where a participant is eligible for multiple domains, the randomisation schedule will allocate that participant to a single intervention within each domain that they are eligible for resulting in them receiving multiple interventions simultaneously across multiple domains. Randomisation will be conducted through a password-protected secure website using a central, computer-based randomisation program. Any further specifics to randomisation required by individual domains are described in their DSA.

8.10. Multifactorial Structure

As the trial may randomise participants in more than one domain it is considered multifactorial. The number of domains which can run concurrently is determined by the interventions that are appropriate and amenable for evaluation within the trial, operational feasibility, and the impact on statistical power as determined by the conduct of simulations. The ability to evaluate interventions across multiple domains simultaneously significantly enhances trial efficiency.

The multifactorial design allows the RECOMMEND Platform Trial to evaluate interactions between selected interventions in different domains. Unless specified in a DSA, the default will

be not to include treatment-by-treatment interaction terms in the primary statistical model and to evaluate interactions as a secondary hypothesis.

Although participants may receive treatment allocations for multiple domains the decision-making regarding concomitant therapies will be made by the treating clinician. Sites will always have final say as to which domains they choose to be involved in.

8.11. Recruitment strategies

8.11.1. Recruitment Overview

The trial is designed to substitute allocation of treatment status by randomisation where otherwise a treatment decision would have been made by clinical staff and for this to occur at the time that the treatment decision would have otherwise been made by procedures at participating units.

Recruitment will be based on the local governance and ethics requirements of each participating site. This will be agreed upon by the coordinating centre (ANZIC-RC) and participating site prior to the commencement of the RECOMMEND Platform Trial and one or more of its domains.

8.11.2. Treatment Allocation

The randomisation program will randomly assign participants to their treatment allocation within each eligible domain.

8.12. Participant Withdrawal

Trial participants may withdraw from the RECOMMEND Platform Trial entirely or from one or more domain-specific interventions.

8.12.1 Participant withdrawal from platform trial

Withdrawal from the entire RECOMMEND Platform Trial occurs when the participant and/or their LAR requests withdrawal from ongoing participation in all RECOMMEND Platform Trial interventions and requests that no trial data be used in any future analyses.

8.12.2 Participant withdrawal from domain-specific interventions

The criteria for withdrawal specific to each domain (i.e., for withdrawal to their randomised treatment within a domain) is outlined in the relevant DSA. Domain specific documentation will track withdrawal information from receiving treatment. Participants and/or LAR who withdraw from all RECOMMEND Platform Trial interventions but allow for the use of their data in the trial will still be considered participants of the RECOMMEND Platform Trial and their data may be used in future analyses.

8.13. Future Domains and Interventions

The RECOMMEND Platform Trial is perpetual. The MC and relevant DSWGs can determine new questions to introduce to RECOMMEND Platform Trial based on real time evidence. This includes adding one or more new interventions to a domain or adding one or more new domains to the platform. Limits on the duration and continuation of a platform trial include:

- availability of ongoing funding
- availability of new interventions to evaluate
- ongoing need to address public health problem/s

All future domains and/or future interventions within a domain will obtain in a HREC and local governance approval prior to commencing at participating sites.

9. DATA MANAGEMENT

9.1. Source Data

Source documents include, but are not limited to, hospital records, clinical charts, laboratory and pharmacy records, imaging, and correspondence.

9.2. Data Collection Methods

9.2.1. Data Collection Personnel

Data can be collected by trained and authorised research personnel at participating sites.

9.2.2. EXCEL Registry Data Collection

Data collected by the EXCEL Registry that is to be linked and used in the RECOMMEND Platform Trial analyses is collected in accordance with the EXCEL Registry's ethically approved process.

9.2.3. Data Collected for the RECOMMEND Platform Trial

Data will be collected in addition to the EXCEL Registry data collection. This data is trial-specific and will be captured in the database and CRF. This data is necessary for the overall functions of the trial.

Platform level data includes:

- Screening and eligibility criteria
- Randomisation data
- Daily data
- Platform Exit data
- Platform withdrawal data
- Protocol Deviations
- AEs
- SAEs/SUSARs

Specific data variables are outlined in section 9.3..

9.2.4. Data Collected for the RECOMMEND Platform Trial's Domains

Each individual domain may require further data collection in addition to that already collected by the EXCEL Registry and collected by the RECOMMEND Platform Trial Core CRFs. Such data must specifically relate to the additional secondary and tertiary outcomes outlined in the relevant DSA. Data collection methods and data variables required will be specified in the DSAs.

9.3. Data Variables Collected

9.3.1. Screening and Eligibility

Data variables required for data linkage with the EXCEL Registry include:

- Patient Initials
- Sex at Birth

- Date of Birth
- Mode of ECMO

Inclusion/Exclusion Criteria is collected during the randomisation process.

9.3.2. Primary Outcome (DOSE)

Data variables relating to the primary outcome (the DOSE outcome) are collected in addition to the EXCEL registry by a RECOMMEND core protocol CRF. Data will be collected from days 1 to 28 inclusive, with day 1 being the day of randomisation. Data variables include:

- Mortality data
- Cardiorespiratory support data:
    - Participant on ECMO
    - Participant invasively mechanically ventilated but without ECMO
    - Participant in ICU but not invasively mechanically ventilated nor on ECMO
- Hospital LOS data:
    - Participant admitted to a hospital
    - Participant discharged from a hospital alive

9.3.3. Platform Exit

Data regarding the reason a patient exits the platform (death, hospital transfer, withdrawal of consent) is collected.

9.3.4. Platform Withdrawal

Platform and Domain-specific withdrawal data is collected for ethical compliance.

- Who withdraws from the platform (patient, legally authorised representative)
- Date of withdrawal
- Method of withdrawal
- Permission for use of data

9.3.5. Protocol Deviations

- Date
- Type of deviation
- Description
- Action Take

9.3.6. Safety Events

- Diagnosis
- Description
- Event Severity
- Date
- Suspected relationship
- Action taken
- Treatment of event
- Outcome
- Outcome
- Domain relationship

9.4. Confidentiality

Trial staff will ensure that the confidentiality of all participants' information will be maintained and preserved at all times. Randomisation occurs through a secure database. The participants will be identified only by a unique trial-specific number on all platform documents and electronic databases visible to the coordinating centre (including outputs and extracts for data analysis).

9.5. Bias Control

9.5.1. Randomisation

Randomisation will be conducted centrally through a password-protected database using a computer-based randomisation program.

9.5.2. Allocation Concealment

Allocation concealment will be maintained by using centralised randomisation in a database that is remote from participating sites.

9.5.3. Blinding of Treatment Allocation

The default position within the Platform is that treatments determined by randomisation will be provided on an open-label basis. However, the blinding of treatment status is not precluded within the Platform. If required, details related to blinding of interventions will be specified in the DSAs.

9.5.4. Blinding of Outcome Adjudication

Wherever feasible, outcome assessment will be undertaken by research staff who are blinded to allocation status of participants. In some instances, blinding may not be possible for the primary outcome and some of the other outcomes within the trial.

9.5.5. Follow Up and Missing Data

Timely validation of data, data queries and data corrections will be performed. Any common patterns of errors found during quality control checks will be fed back to participating sites. If values necessary for the Bayesian modelling of the primary endpoint are missing they may be imputed using available data. Additional details are provided in the Statistical Appendix.

9.6. Data Access and Ownership

9.6.1. Data Ownership

All RECOMMEND specific data is owned by the sponsor under the custodianship of the MC. EXCEL Registry data relating to the RECOMMEND platform is owned by EXCEL Registry data custodian/s in accordance with the registry's ethical requirements. Storage and archiving of hard-copy study documents (CRFs and consent forms) will be the responsibility of the PI at each site and will remain at the site of recruitment following local security guidelines. Hard-copy study documents will be kept for a minimum of 15 years and confidentially destroyed at the end of this period only with the express consent of sponsor/coordinating centre.

9.6.2. Access to Data

Access will be granted to authorised representatives from the MC, sponsor, any host institution/s and the regulatory authorities to permit trial-related monitoring, audits and

inspections. The coordinating centre will comply with all relevant jurisdictional and academic requirements relating data access through ANZIC-RC standard data access procedures.

9.7. Co-enrolment with Other Trials

Co-enrolments with other trials will be considered on a case-by-case basis by the MC through a mutual acknowledgement between both studies that co-enrolment is allowed. Co-enrolment will typically be sought per domain operating in the RECOMMEND Platform Trial.

9.8. Concomitant Care and Co-interventions

All treatment decisions outside of those specified within the RECOMMEND Platform Trial will be at the discretion of the treating clinician/s. Prespecified co-interventions between trials related to specific domains will be recorded in the relevant DSA where applicable.

10. ETHICS AND GOVERNANCE

10.1. Ethical Conduct

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration (TGA) comments, and the NHMRC National Statement on Ethical Conduct in Research Involving Humans 2023.

10.2. Management of Participating Sites and Trial Coordination

The coordinating centre takes primary responsibility for the management of participating sites, data management for participating sites, reporting of significant safety events to the DSMC and HREC (where applicable) and providing web-based randomisation.

10.3. Human Research Ethics Committee (HREC) Review

All areas of the protocol (including individual DSAs) for this trial will be reviewed by a lead HREC. Each PI will then be responsible for applying for local research governance approval at each participating site.

Any amendment to already approved trial documentation will be submitted for review by the lead HREC and only implemented after receiving both HREC and local governance approvals at each site, unless the change is necessary to eliminate an immediate hazard to patients. The HREC will be informed of such changes as soon as possible. The PI will also be responsible for submitting progress reports, SAE reports, and any other required documentation to the coordinating centre, MC or their local governance offices in accordance with their guidelines. Copies of all HREC and research governance office correspondence will be provided to the coordinating centre together with a copy of the approved consent documents where applicable. Copies of the same documents will also be kept with the study investigator site files.

10.4. Ethics and Regulatory Issues

All patients enrolled in this trial will lack capacity to give consent at the time of trial enrolment due to their critical illness. Additionally, many interventions within this trial must be initiated urgently, either because the intervention is time-critical or because the most valid evaluation of

the intervention occurs if the trial intervention is initiated at the same time-point as would occur in clinical practice. The following consent options are acceptable in this setting:

(i) waiver of consent;
(ii) (ii) consent to continue
(iii) (iii) opt-out process
(iv) (iv) consent provided by an ethics committee
(v) (v) Guardianship Board or other legal authority.

Which options are available at individual participating sites will be determined by the relevant ethics committee and/or administrative tribunals and subject to applicable laws in each participating jurisdiction.

As each Domain has specific requirements based on the interventions, each DSA will outline the process for consent that apply to that domain and jurisdiction/s.

10.5. Inclusion of Participant Data in Analyses

The multifactorial nature of the platform trial creates issues related to withdrawal of consent by participants and/or their LAR after randomisation. Participants and/or their LAR may withdraw consent for participation in the platform trial at any time. Participants and/or their LAR may withdraw consent for continued receipt of interventions in one or more domains of the trial in which they have received an allocation. They may permit the use of data collected and permit the data to continue to be collected. Participants and/or their LAR may withdraw consent for the future collection of data but allow for the use of data up until the date of withdrawal.

In some instances, participants and/or their LAR are also given the option to withdraw permission for the use of all platform trial data, including platform trial data that has already been collected. For the RECOMMEND Platform Trial it is not possible to withdraw consent for collection and use of platform trial data from one or more domains while permitting the collection and use of platform trial data for other domains.

All participants who withdraw consent for use of platform trial data will be reported in a CONSORT patient flow diagram, as per CONSORT requirements. A participant who withdraws consent for participation in an intervention allocated by the trial, but does not withdraw permission for data use, will be reported in CONSORT patient flow diagrams as having been randomised in that domain and, to abide by the intention to treat (ITT) principle, will be analysed in that domain.

Participants will be excluded from analyses if, at the time of the creation of the analysis dataset, it is known that consent has been withdrawn for participation in all domains in which they have received an allocation, and for the use of their data. In addition, participants will be excluded if they have been enrolled under a delayed consent model (e.g. consent to continue) but consent cannot be obtained and ethical approvals do not permit the use of participant data without consent for that domain.

It is not possible to remove a participant's data retrospectively after an analysis that has been used for Public Disclosure. Therefore consent data and any withdrawal of consent will be recorded on the CRF to ensure data is appropriately included or excluded from future analyses.

10.6. Approvals

The protocol, information brochures, consent forms, and participant and/or LAR information sheets will be submitted to the lead HREC as required. Participating sites will submit ethically approved documents to their local governance offices as required. Each participating site will submit this protocol and any other relevant study documentation reviewed by the HREC to their local governance office. Governance must be approved at each individual site prior to that site commencing recruitment.

10.7. Protocol Amendments

All protocol amendments to the Core Protocol and DSAs will be submitted for approval to the lead HREC. Following lead HREC approval participating sites must submit amended documents to their local governance office for local approval.

Where the cessation of an intervention or domain occurs then randomisation to that intervention or domain will no longer be available. Cessation of an intervention or domain will be reported to all relevant regulatory bodies.

11. STATISTICAL PROCESS

A description of how the statistical analysis will be conducted for reporting treatment effects (including the statistical models, approaches to reporting, statistical adaptations and decision criteria) will be presented in the Domain-specific Statistical Analysis Plans (DSSAPs).

The Core Adaptive Design Report (ADR) describes the generic elements of the statistical design which apply to all domains in the platform, and provides generic operating characteristics (obtained vis simulations) for the default design of a two-arm domain. An individual domain may have a domain-specific ADR that defines domain-specific design features including additional key endpoint(s), adaptations, statistical modelling/triggers, and operating characteristics. The status of the platform at any point in time will be included in a separate Current State of the Statistical Models document.

11.1. Statistical Approach of the Study Design

Within the RECOMMEND Platform Trial, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are conducted over time on the accumulated outcome data to determine within strata if:

- An intervention is superior;
- An intervention is inferior;
- An active intervention is futile compared to the standard of care

Every participant will be assigned a set of interventions, comprising one intervention from each domain for which the participant is eligible. The combination of interventions to which a participant is assigned comprises the regimen and the regimens are the available treatment arms in the trial. Participants will be classified by membership in different populations defined by one or more strata. The unit-of-analysis for a domain is the most granular level, defined by one or more stratum, within which the treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain.

11.1.1. Bayesian Statistical Modelling Overview

Inferences in this trial are based on a Bayesian statistical model of the primary outcome of the DOSE score. This will calculate the probability of superiority, inferiority, and futility of the interventions (using the posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, considering the evidence accumulated during the trial (based on the primary outcome data of participants) and on assumed prior knowledge (known as a prior distribution) [11,12]. For the evaluation of the main effects of interventions within a domain, the default design assumes that parameters in the model have a weakly informative, neutral prior distribution. This means that any subsequent Platform Conclusion is not influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e. it is the most conservative approach, making no assumptions regarding the direction of the treatment effect).

The main effect in the model is the treatment effect of each intervention. Each stratum, or combination of strata is analysed separately but the model captures the commonalities (regarding the treatment effect) across such sub-groups. Additionally, and where specified, the statistical model allows evidence relating to the effectiveness of an intervention in one stratum to contribute (via 'borrowing') to the estimation of the posterior probability distribution (of the effectiveness of an intervention) in other strata, but this only occurs to the extent that the treatment effect is similar in different strata.

When a Platform Conclusion is achieved, the results derived from the model, including any contribution from borrowing, will be reported. It is acknowledged that the estimate of the treatment effect for a stratum may be contributed to by borrowing from adjacent strata but the results from the strata that have contributed to borrowing will not be reported, unless the other strata have simultaneously reached a Platform Conclusion. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions and, where specified, the extent to which that effectiveness varies between strata (intervention-stratum interaction).

11.1.2. Simulations and Statistical Power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive simulations using standard Monte Carlo methods. Simulations may be updated when a new intervention is added within a domain or whenever a new domain is added to RECOMMEND Platform Trial. The results of the simulations used to inform the design of a domain will be reported within the Statistical Appendix (ADR).

11.1.3. Statistical Handling of Ineligible Participants

The goal of the RECOMMEND Platform trial is to enrol as wide a participant population as possible. Because of this and the desire to explore multifactorial regimens it will not be uncommon that a participant will be ineligible for single interventions or entire domains, or interventions may be temporarily unavailable for use. In this section we present the details for how the RECOMMEND Platform Trial deals with these possible circumstances.

If an intervention is unavailable at the time of randomisation due to site restrictions (for example, exhausted supply or unavailable machinery) then the participant will be randomised among all remaining interventions that are available and this participant will be included in the primary analysis set as though they were randomised unrestricted to their assigned intervention.

If a participant is ineligible for an entire domain then that participant will not be randomised to an intervention from that domain. The participant will be randomised to a regimen from all

remaining domains that they are eligible for. As long as the participant is randomised within at least one domain they will be included in the primary analysis. For the ineligible domain, the participant will be assigned a covariate for that domain reflecting ineligibility. This allows the model to learn about the relative efficacy of the remaining interventions in the domains in which the participant has been randomised. If there is a domain with only two interventions and a participant is ineligible for one of the two then the participant will be treated as though they are ineligible for the domain. If there is a domain with more than two interventions but a participant is ineligible for all but one then the participant will be deemed ineligible for the domain.

If there is a domain with more than two interventions and the participant is ineligible for at least one due to a patient-level factor (for example known intolerance to an intervention), but eligible for at least two, then the participant will be randomised among those interventions that the participant is eligible to receive. The participant will have their assignment included in the primary Bayesian model with an appropriate covariate identifying their ineligibility status that considers that a patient-level factor that determines partial eligibility could be associated independently with outcome. The impact of participants with partial eligibility will be taken into consideration by the DSMC at the time of consideration of whether a Platform Decision is appropriate following a Statistical Trigger.

11.2. Stratum Management

A covariate in The RECOMMEND Platform Trial that can be used as a unit-of-analysis within a Bayesian statistical model that allows for the possibility of differential treatment effects for different levels of the variable is referred to as a stratum. The covariate is classified into mutually exclusive and exhaustive sets for analysis of treatment effect. The criteria that define a stratum are based on a characteristic that is present at or before the time of enrolment. DSAs will specify each stratum for analyses in their respective domains.

The simplest structure for strata is a single dichotomous baseline variable, which divides participants in The RECOMMEND Platform Trial into two strata. More complex arrangements are possible, such as a single strata variable that is ordinal or two (or more) dichotomous or ordinal strata variables, the combination of which defines a single stratum (i.e. there are ≥ 2 strata when there are N dichotomous stratum variables).

An important platform-wide stratum is the type of ECMO the patient is on at time of randomisation, categorised as VA (including eCPR) or VV ECMO. These stratum levels are is used for all platform domains unless otherwise specified in the relevant DSA.

The number of strata variables and the number of strata within The RECOMMEND Platform Trial may be varied, depending on the impact of such decisions on statistical power, as determined by simulations, and the clinical relevance of each strata to answer a particular research question for each domain. The modelling of strata may assume no differential effect for some domains. This may occur in two ways. Firstly, when the strata structure defines the entry criteria for a domain. Secondly, when two or more stratum are combined within a single unit-of-analysis (i.e. the unit-of-analysis comprises two or more stratum). If the unit-of-analysis comprises less than all available strata the analysis that is performed assumes that treatment effect does not vary between stratum combined within a common unit-of-analysis.

11.2.1. Treatment-by-strata Interactions: Borrowing Between Strata

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different strata. A Bayesian Hierarchical Model is used for all treatment-by-strata interactions. In this, a hyperprior is specified on the standard deviation of treatment effects

across strata. Different prior distributions will result in different levels of borrowing. Priors can be selected to incorporate strong, weak, or moderate statistical borrowing. The specific prior used for treatment-by-strata effects will be specified in each DSSAP.

11.3. Adaptive Analyses

Frequent adaptive analyses using Bayesian statistical methods will be undertaken using Markov Chain Monte Carlo (MCMC) estimates of the Bayesian posterior probability distributions [12]. The trial will utilise a set of pre-specified rules to reach conclusions regarding the effectiveness of interventions that are being evaluated. It is these pre-specified rules that determines how the trial "adapts" to the information contained in accumulating participant data. An analogy is that the 'routes' that a trial can take are pre-specified, within the protocol, but the exact route that the trial takes is determined by the data that accrues. Such adaptation improves statistical efficiency and patient safety substantially.

11.3.1. Determining Inferences of Results with Adaptive Analyses

Inference in the RECOMMEND Platform Trial is determined by analyses using pre-specified statistical models that incorporate adjustments for covariates which may be associated with the primary endpoint. These models incorporate variables that represent each intervention assigned to participants. The efficacy of each intervention within a domain may be modelled as not varying in across any of the strata, or possibly varying in one or more of the different strata in RECOMMEND Platform Trial. Where the efficacy of each intervention within a domain is modelled as possibly varying, borrowing between strata is permitted. The unit-of-analysis that will be modelled may comprise the entire population (i.e. no categorisation by strata is applied) or may be defined by one or more stratum. The unit-of-analysis and whether borrowing can occur between strata is pre-specified for each domain. At each analysis the current version of the statistical model is used, and may include patients who were enrolled when previous versions of the model were being used. The current model is described in an operational document (from the Current State document), maintained by the blinded statistical design team. Unless otherwise specified modifications and implementation of modifications to the model require the approval of the RECOMMOEND Platform Trial MC and do not require a protocol amendment.

11.3.2. Triggers for Adaptive Analyses

Whenever a model hits a predefined threshold for any of superiority, inferiority, or futility for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more strata and will be reviewed immediately by the DSMC. When a Statistical Trigger is confirmed by the DSMC, based on a thorough review of the data including an evaluation of the proportion of patients for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion, then a declaration of a Platform Conclusion occurs. The declaration of a Platform Conclusion will lead to appropriate modification of the interventions available within that domain and a Public Disclosure of the result. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain.

11.3.3. Statistical Trigger for Intervention Superiority

In general, at any adaptive analysis, if a single intervention has at least a 0.98 posterior probability of being the optimal intervention, for that unit-of-analysis, then that intervention will be deemed as being superior in that domain and target population. In a two-arm domain, the posterior probability of being the optimal intervention is equivalent to having an odds ratio

greater than 1 relative to the control intervention in the domain (where an odds ratio >1 indicates treatment benefit of the intervention).

11.3.4. Statistical Trigger for Intervention Inferiority

In general, at any adaptive analysis, if a single intervention has less than a 0.02/(J-1) posterior probability of being the optimal intervention in the domain, for a unit-of-analysis, then that intervention will be deemed as being inferior for that target population, where J is the number of active/remaining interventions in the domain. If superiority and inferiority were to be discovered simultaneously (for example when there are two interventions), the result will be interpreted as demonstrating superiority.

11.3.5. Statistical Trigger for Intervention Futility

In general, at any adaptive analysis, if an active intervention has a less than 0.05 posterior probability of having an odds ratio greater than 1.15 relative to the control intervention in the domain, for a unit-of-analysis, then that intervention will be deemed as being futile for that target population.

11.3.6. Statistical Trigger is Achieved

If a Statistical Trigger is achieved this will be communicated by the SAC to the DSMC. Subject to the DSMC confirming that a Statistical Trigger has been reached validly, the DSMC will oversee a range of actions, as follows.

11.3.7. Actions Following Statistical Trigger for Superiority

If an intervention triggers a threshold for superiority and the DSMC declares this as a Platform Conclusion, the intervention is deemed as being superior. The result will be communicated to the MC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

11.3.8. Actions Following Statistical Trigger for Inferiority or Futility

If the trial triggers a threshold for inferiority or futility and the DSMC declares this as a Platform Conclusion, the intervention is deemed as being inferior or futile. The result will be communicated to the MC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

11.4. Analysis of Data to Reach Conclusions

The Core Protocol sets out the default pre-specified rules for interpreting the results of analyses. These rules include (default) pre-specified threshold levels of probability for achieving superiority, inferiority or futility of interventions within a domain. However, some domains may choose to use a separate set of pre-specified rules, which will be specified in the relevant DSAs. At each adaptive analysis the SAC evaluates whether one or more probability thresholds derived from the trial's statistical model have been exceeded. When the model indicates one or more of superiority, inferiority, or futility has occurred, this is termed a Statistical Trigger. A Statistical Trigger may be reached for one or more strata at any given adaptive analysis.

The occurrence of a Statistical Trigger is communicated immediately to the trial DSMC by the SAC. The DSMC has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of the inferior intervention(s) from randomisation options or removal of all other interventions in a domain if an intervention is declared as superior. A Platform Conclusion will be communicated

to the MC who have responsibility for dissemination of the result/s by presentation, publication and communication/s with all relevant stakeholders.

The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrolment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also helps avoid indeterminate results by continuing randomisation until a stopping rule is met. [11-13] An additional advantage is that dissemination of such results does not interrupt the conduct of the platform.

11.4.1. Analysis Set for Reporting

The primary analysis set that will be used for reporting a Public Disclosure will comprise all participants who are randomised at the time of the adaptive analysis resulting in the Statistical Trigger.

12. HEALTH ECONOMIC ANALYSIS

The conduct of a health economics analysis can occur after recruitment to an intervention group and/or a domain is halted. Whether a health economics analysis is conducted following halting of a single intervention in a domain will be determined by the DSWG in conjunction with the MC, based on the rationale for a cost-effectiveness analysis in an ongoing domain. A detailed description of how the health economic analyses will be conducted for reporting the cost-effectiveness of interventions will be presented in the Health Economics Appendix to the Core Protocol and the Domain-specific Health Economic Analysis Plans (HEAP) as appropriate. In brief, the primary cost-effectiveness analysis for an intervention and/or a domain will determine the cost per QALY of an intervention using a time-horizon of 180 days and a healthcare payer perspective. Resource use items collected within the trial (e.g., organ support, index ICU and hospital length of stay) will be assigned unit costs. The cost-effectiveness for each treatment comparison will be reported in terms of incremental cost-effectiveness ratios, net monetary benefit, and cost-effectiveness acceptability curves. The reporting of health economics results will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).

13. QUALITY ASSURANCE

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP) and relevant regulations.

13.1. Protocol Adherence and Data Completeness

Data management and data management support (such as query resolution) will be coordinated by the RECOMMEND project and data management teams.

Several procedures to ensure data quality and protocol adherence will be undertaken. These include:

- A start-up meeting for all research staff and investigators that will be held prior to study commencement to ensure consistency in procedures
- A detailed dictionary will define the data to be collected on the Platform and DSA CRFs
- Timely validation of data and query resolution will be performed by the coordinating centre.
- Data monitoring (as described below)

13.2. Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved trial that is not consistent with the research protocol or consent document. A protocol deviation may be an omission, an error, addition or change in any procedure described in the protocol.

A protocol deviation in RECOMMEND is defined as an event where protocol specified tasks or activities did not occur or where interventions were affected to the extent that is outside of the intended process within the core protocol or relevant DSAs.

14. DATA MONITORING

14.1. Data Monitoring & Missing Data

Trial personnel will perform timely validation of data, queries and corrections. Any common patterns of errors found during quality control checks will be fed back to all sites. If values necessary for the Bayesian modelling of the primary endpoint are missing, they may be imputed using available data.

The study will be monitored by a representative of the coordinating centre. A site initiation teleconference or visit will be conducted before site activation. Routine monitoring visits will be conducted as outlined in the data monitoring plan. The data monitoring plan is an operational document that will be drafted and finalised prior to recruitment. Email and telephone communication will supplement site visits.

14.2. Data Safety & Monitoring Committee

A single DSMC will be responsible for safeguarding the interests of trial participants and assessing the safety and efficacy of the trial.

14.2.1. Members

The DSMC will have member/s with experience in adaptive clinical trial design, platform trials, and well as critical/intensive care medicine. The DSMC will consist of the chair as well as additional medical, statistical, and other experts to ensure all necessary expertise to oversee a trial of this complexity and scope.

14.2.2. Activities & DSMC Charter

The DSMC will conduct its activities in accordance with this core protocol, relevant domains, and the DSMC charter. The DSMC Charter will be approved by DSMC prior to the initiation of the trial. The DSMC charter is an operational document agreed upon between the DSMC and the MC. The DSMC Charter outlines the roles and responsibilities of the MC, DSMC, and data management and statistical teams involved in the trial.

14.2.3. Blinding

The DSMC will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

14.2.4. Roles & Responsibilities

The DSMC will review updates of the trial's analyses from the SAC. The DSMC will

- Monitor evidence for treatment harm and compliance with the protocol
- Ensure that the pre-specified trial algorithm is being implemented as designed
- Ensure that the trial design remains appropriate from a scientific and ethical point of view

The DSMC will be advisory to the RECOMMEND Platform MC and all relevant DSWGs. The RECOMMEND Platform MC and all relevant DSWGs will be responsible for promptly reviewing the DSMC recommendations. The RECOMMEND Platform MC and all relevant DSWGs decide whether to continue or discontinue treatments within a domain, and determine whether amendments to the protocol or changes in trial conduct are required.

15. SAFETY MONITORING AND REPORTING

15.1. Overview

This section outlines procedures for defining, assessing, documenting and reporting safety events that may occur in participants enrolled in the RECOMMEND Platform Trial.

The safety monitoring and reporting framework is consistent with the NHMRC National Statement on Ethical Conduct in Human Research, ICH GCP (E6[R2]), The Australian Clinical Trial Handbook, and TGA pharmacovigilance guidelines.

15.2. Definitions

Adverse Event (AE)	AEs are defined as any untoward medical occurrence in a participant or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship (be attributable) to trial interventions or participation. (adapted from the *Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95* July 2000)).
Serious Adverse Event (SAE)	An AE that: • Results in death (e.g. septic shock) • Is life-threatening (e.g. cardiac arrest) • Is a medically important event • Results in prolongation of existing hospitalisation • Results in the participant becoming permanently/significantly disabled/incapacitated • Results in a congenital abnormality or birth defect
Reference Safety Information (RSI)	The source documentation used to determine the expectedness of a safety event. The RSI may be found in: • The Investigator's Brochure (for investigational products) • The Product Information (for approved medicines used off-label) • This core protocol or relevant DSAs for other trial interventions

Severity	Severity refers to the measure of intensity, not the clinical outcome. E.g. a *severe* electrolyte imbalance may not be 'serious' if quickly rectified and there is no lasting consequence.
Seriousness	Seriousness is defined by the outcome of a safety event. E.g. a mild allergic reaction that, if left untreated, results in prolonged hospitalisation of an existing ICU admission.

15.3. Principles of Safety Events in Critical Care Research

The principles used in the conduct of safety monitoring and reporting in this trial are those outlined in the manuscript *Serious adverse events in academic critical care research.*[14]

A high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. Patients who are critically ill, irrespective of whether or not they are enrolled in a trial, will typically experience events (e.g. renal failure, shock, cardiac arrest, death) that would meet the conventional definition of a safety event.

Therefore, safety events of all severity will only be reported by site PI and/or their authorised delegates if it is believed the events are attribute to the trial interventions and participation.

This is common practice amongst critical care studies.

The strategy outlined for the attribution and reporting of safety events in this platform is designed to:

- Capture safety events that, on reasonable grounds, are believed to be attributable to trial interventions and trial participation
- Avoid reporting of safety events likely to be part of the natural course of critical illness

15.4. Attributions of Safety Events to Trial Intervention/Participation

15.4.1. Attribution of Safety Events to Trial Interventions or Trial Participation

It is possible that participants within the trial will experience various health or medical events that could be attributed to one or more study interventions. It is often difficult to distinguish between events that occur as a consequence of the general course of critical illness and interventions specified by the trial.

For the RECOMMEND Platform Trial, a safety event will be considered attributable if, in the opinion of the PI or delegates, it is reasonably related to trial interventions or participation and cannot be solely explained by the expected progression of critical illness or standard clinical care.

15.4.2. Attribution of a Death to Study Interventions or Trial Participation

Critically ill patients who will be enrolled in this trial are at high risk of death. Death is a high risk in the ECMO patient population. Death data will be tabulated and reported to the DSMC as well presented in any manuscript. Deaths that are determined to be attributable to trial intervention/s or participation are required to be reported as an SAE.

15.5. Assessment of Safety Events

Each potential safety event must be assessed for:

1) Severity
2) Seriousness
3) Attribution (relatedness)

And serious adverse safety events are to be assessed for:

4) Expectedness

The PI and/or their delegates are required to assess severity, seriousness and attribution of all safety events.

Assessment of expectedness will be performed by the trial MC or relevant DSWG's delegated independent medical monitors based on the specified RSI.

15.5.1. Severity

Each event severity is graded by the site PI and/or their authorised delegates.

Severity is to be classified as mild, moderate, or severe.

15.5.2. Seriousness

In accordance with the NHMRC's 2016 guidance on *Safety Monitoring and Reporting in Clinical Trials,* the PI and/or their delegates should classify a safety event as serious if the outcome of any safety event:

- Results in death
- Is life-threatening
- Is a medically important event
- Results in prolongation of existing hospitalisation
- Results in the participant becoming permanently/significantly disabled/incapacitated
- Results in a congenital abnormality or birth defect

15.5.3. Attribution (Relatedness)

Attribution is determined by the site PI and/or their authorised delegates. The PI or delegates will make judgement as to whether a safety event is attributable to trial interventions or participation

The PI and/or their delegate's opinion of the relationship between the safety event and the trial interventions/treatments are specified as:

Not related	The event is not attributable
Unlikely	The association between the interventions and the safety event is such that the interventions are not likely to have any reasonable association

Possibly	The safety event could have been caused by the interventions
Probably	The safety event follows a temporal sequence from the time of intervention and cannot be reasonable explained by the known characteristics of the participant's presentation/history
Definitely	The safety event follows a reasonable temporal sequence from the time of intervention or reappears when the interventions are repeated

15.5.4. Expectedness

Expectedness of a safety event involves evaluating whether the event is anticipated based on the known safety profile of the interventions, the underlying critical illness, and clinical context.

AEs are not required to be assessed for expectedness.

All reported SAEs are to be assessed for expectedness by the RECOMMEND MC/relevant DSWG independent medical monitors based on the RSI.

15.6. PI and/or Authorised Delegate Reporting

The PI and/or their authorised delegates are required to report safety events of all severity that, on reasonable grounds, are attributable to trial interventions and participation and cannot solely be explained by the natural course of critical illness.

The PI and/or their authorised delegates are not required to report safety events that are not attributable to trial interventions and participation.

This is consistent with sections 15.3 and 15.4 of this core protocol.

15.6.1. Reporting Procedures for AEs

There is no mandated time frame under Australian guidelines for reporting AEs however it is expected that the PI or delegate will report attributable AEs within 72 hours of becoming aware of the event (as per standard practice for critical care trials)

All recorded AEs will be reviewed periodically by the coordinating centre and relevant DSWGs that the AEs apply to.

15.6.2. Reporting Procedures for SAEs

SAEs that are considered to be attributable to a trial intervention or participation must be reported to the coordinating centre within 24 hours of the site staff becoming aware of the event. This is reportable via the trial database.

These should be reported only where, in the opinion of the PI or delegate, the event might have reasonably occurred as consequence of a trial interventions or participation and cannot solely be explained by the natural course of critical illness.

Events that are not considered attributable to trial interventions or participation do not require reporting to the coordinating centre.

15.7. Coordinating Centre Reporting

The coordinating centre will oversee safety reporting and ensure that relevant information is provided to the DSMC and other bodies in accordance with ethical requirements and national standards.

15.7.1. AE Reporting to DSMC

Aggregated AE data will be provided to the DSMC and reviewed periodically for potential safety signals.

15.7.2. SAE Reporting to DSMC

Expected SAEs will be tabulated, reviewed and provided to the DSMC at the time of each analysis as specified in the DSMC Charter.

Unexpected SAEs will be reported to the DSMC on an individual basis within 7 calendar days of receipt from the site.

16. FUNDING OF THE TRIAL

The Medical Research Future Fund (MRF2023109).

17. TRIAL REGISTRATION

Local Trial Registration Number: ANZIC-RC/CH006.
Universal Trial Number (UTN): NCT06526533.

18. PUBLICATION POLICY

Manuscript(s) and abstract(s) resulting from the data collected during this study will be prepared by the corresponding DSWG. Where results are influenced by interaction between domains, the DSWG for both domains will take responsibility for preparation of manuscripts and abstracts. All manuscripts and abstracts reporting trial results that are prepared by one or more DSWGs must be submitted to and approved by the RECOMMEND MC before submission.

Site investigators will not publish or present interim or definite results, including but not restricted to oral presentations without permission from the MC.

The role of site investigators and RCs at participating sites will be acknowledged by their names being listed as collaborators. Where required publications will comply with the publication policies of clinical trials groups that have endorsed or supported the study and the ANZIC-RC.

19. VERSION INFORMATION

Version	Changes	Date
1.0	N/A	23/09/2024
2.0	• Addition of Data Management Centre, Independent Statistical Team and Health Economics Working Group to the platform's administration structure • Clarification around the levels of participant withdrawal from the platform and from domain-specific appendices • Refined data variables collected • Refined statistical processes • Addition of health economic analyses section • Refined safety monitoring and reporting procedures	21/07/2025

19.1. Management Committee Authorisation

The RECOMMEND Platform Trial MC have approved the present protocol version noted above, and authorise it as the most current official protocol.

19.1.1. Approval Signature of Core Protocol

RECOMMEND MC Chair: Prof Carol Hodgson

Signature:  **Date:** 21/07/2025

Organisation: Monash University

Department: ANZIC-RC

Position: Coordinating Principal Investigator

Telephone no.: +61 437 609 861

Email: Carol.hodgson@monash.edu

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