Clinical Trial Protocol- Australian Sites

Version 1.0

15 April 2024

The Threshold for Platelets study (T4P): a prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure.

ISRCTN Registry Number: ISRCTN79371664

This study is supported by the Australia and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)

Contents

1 Synopsis

Title	The Threshold for Platelets study: a prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure.
Short title	Threshold for Platelets (T4P)
Trial registration	ISRCTN Registry Number: ISRCTN79371664
Background	Prophylactic platelet transfusions are frequently administered to critically ill patients with low platelet counts to reduce the risk of bleeding before they undergo a procedure. However, evidence to support this practice is poor. It is unclear whether pre-procedure prophylactic platelet transfusions reduce bleeding or are otherwise beneficial to ICU patients, and there is evidence that platelet transfusion can cause patient harm. In addition, platelets collected for transfusion are expensive and in limited supply.
Aim	To define the optimum platelet threshold below which platelets should be transfused prior to an invasive procedure in critically ill patients, and to explore whether the optimum threshold differs according to patient characteristics.
Objectives	1. To model the threshold-response curve for the effect of platelet transfusion prior to/during an invasive procedure in critically ill patients. 2. To evaluate whether the optimum value of the threshold-response curve varies according to patient characteristics. 3. To evaluate the cost-effectiveness of standardisation of practice to the optimum threshold versus current usual practice, including an Australian economic evaluation.
Study design	Open label, randomised, Bayesian adaptive comparative effectiveness trial across five equally spaced thresholds of thrombocytopenia (<10 - <50 x 10^9/L).
Participants and sites	1. Critically ill adults admitted to, or requiring admission to, an ICU who have low platelet counts (<50 x 10^9/L) prior to a low bleeding risk invasive procedure. 2. 2,550 ICU patients worldwide, 500 of whom will be recruited from 20 Australian ICUs.
Inclusion criteria	1. Adult (aged ≥ 18 years) 2. Accepted for admission or admitted to a participating ICU 3. Platelet count < 50 x 10^9/L 4. Planned to undergo a **specified** low bleeding risk invasive procedure OR platelet transfusion considered for an **'other'** low bleeding risk procedure **Specified** low bleeding risk invasive procedures include the following:

	• CVC insertion (including vascular access for renal replacement therapy) • Paracentesis/superficial abdominal fluid collection drainage • Pleural aspiration **'Other'** procedures may be included if the clinician deems these to be a low bleeding risk invasive procedure and a platelet transfusion is being considered for the procedure. These include, but are not limited to: • Arterial catheter insertion • Arterial or central venous catheter removal • Pleural drain • Interventional radiology • Bronchoscopy with or without lavage • Wound dressing changes • Surgical procedures where the clinical team agree risk of bleeding is low, e.g. re-look laparotomy, or wound closure
Exclusion criteria	1. Ongoing major haemorrhage requiring blood products and/or surgical/radiological intervention† 2. Intracranial haemorrhage within prior 72 hours† 3. Contra-indication to platelet transfusion (such as thrombotic microangiopathies; heparin-induced thrombocytopenia; immune thrombocytopenia; congenital platelet function defects) 4. Acute promyelocytic leukaemia (APML) 5. Known advance decision refusing blood/blood component transfusions (e.g. Jehovah's Witnesses) 6. Death perceived as imminent or admission for palliation 7. Previously randomised into T4P 8. Fulfilled all the inclusion criteria and none of the other exclusion criteria ≥ 72 hours †Exclusion criteria 1 and 2 are dynamic, if resolved, the patient may be reconsidered for the trial.
Intervention	Patients will be randomised to one of five equally spaced platelet thresholds (<10 - <50 x 10^9/L) below which they would receive a single adult equivalent dose (AED, defined according to national specifications) of platelet transfusion delivered before or during the procedure.
Outcomes	**Primary outcomes:** • Clinical effectiveness: All-cause mortality at 90 days • Cost-effectiveness: Incremental costs, QALYs and net monetary benefit at 90 days **Secondary outcomes:** • Mortality at discharge from ICU, hospital and at one year • Survival to longest available follow-up

	• Rates of major and fatal bleeds classified according to the HEmorhage MEasurement (HEME) bleeding score • Venous and arterial thromboses in hospital and to one year • Duration of renal, advanced cardiovascular and advanced respiratory support • Length of critical care unit and acute hospital stay • Health-related quality of life (QoL, EQ-5D-5L questionnaire at 90 days and one year) • Resource use and costs at 90 days and one year • Net monetary benefit at one year

2 Abbreviations

AE	Adverse event
AED	Adult Equivalent Dose
ANZICS	Australia and New Zealand Intensive Care Society
APML	Acute promyelocytic leukaemia
ATMG	Australian trial management group
ATWP	Australian trial working party
CCMDS	Critical Care Minimum Data Set
CEA	Cost-effectiveness analysis
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTG	Clinical Trials Group
CTU	Clinical Trials Unit
CVC	Central venous catheter
DMEC	Data Monitoring & Ethics Committee
EQ-5D-5L	European Quality of Life Scale
GCP	Good Clinical Practice
HAT	Hospital-acquired (or -associated) Thrombosis
HEME	Haemorrhage measurement bleeding score[1]
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HREC	Human Research Ethics Committee
HrQoL	Health-related quality of life
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive care unit

ISRCTN	International Standard Randomised Controlled Trial Number
LOS	Length of Stay
MBS	Medicare Benefits Schedule
MRC	Medical Research Council
MRFF	Medical Research Future Fund
NHMRC	National Health & medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
NMB	Net monetary benefit
PBS	Pharmaceutical Benefits Schedule
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PR	Person responsible
QALY	Quality-adjusted life year
RCT	Randomised Clinical Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
TSC	Trial Steering Committee
T4P	Threshold for Platelets
TIDieR	Template for Intervention Description and Replication
UK	United Kingdom
VTE	Venous thromboembolism

3 Administrative information

3.1 Central (international) and UK trial coordinating centre

Coordinating Centre:
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3.2 Australian coordinating centre

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Sponsor:	The University of Queensland Brisbane Queensland 4072
Funder:	Medical Research Future Fund (MRFF) International Clinical Trial Collaborations grant (2031827)

3.3 Australian Trial Working Party

The Australian Trial Working Party (ATWP) will be responsible for overseeing all aspects of the Australian conduct of the trial including the day-to-day management, reporting, ethical approval, financial management, governance, and regulatory compliance for all Australian sites, and will liaise closely with the UK-based central coordinating centre and Trial Management Group. Meetings of the ATWP will be held regularly as required to ensure effective oversight.

3.3.1 Members

Ms Christine Brown	Australian Project Manager
Dr Elissa Milford	Senior Lecturer, The University of Queensland, Qld, Australia Staff Specialist, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia
Prof Michael Reade	Head, Greater Brisbane Clinical School, University of Queensland Pre-eminent Staff Specialist, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia
Prof Erica Wood	Co-director, Division of Acute & Critical Care, School of Public Health & Preventive Medicine, Monash University Consultant clinical and laboratory haematologist at Monash Health

Prof Zoe McQuilten	Consultant Haematologist, Monash Health Deputy-director Transfusion Research Unit, Monash University
Prof Craig French	Director of Intensive Care, Western Health Clinical Professor, The University of Melbourne
Ms Belinda Howe	Senior project manager, ANZIC Research Centre, School of Public Health & Preventive Medicine, Monash University
Dr Lisa Higgins	Health Economics Senior Research Fellow, ANZIC-RC, Monash University
Ms Hayley Noble	UK Trial Manager, Intensive Care National Audit & Research Centre
Ms Daisy Lindsay	Research Coordinator, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia

3.4 Australian Trial Management Group

The Australian Trial Management Group (ATMG) will be responsible for overseeing the management of the trial including the financial management, development and approval of the protocol and study materials, and reporting to funding and regulatory bodies. Meetings of the Trial Management Group will be held quarterly, or more frequently during key stages of the trial, to ensure effective communication.

3.4.1 Members

Ms Christine Brown	Australian Project Manager
Dr Elissa Milford	Senior Lecturer, The University of Queensland, Qld, Australia Staff Specialist, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia
Prof Michael Reade	Head, Greater Brisbane Clinical School, University of Queensland Pre-eminent Staff Specialist, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia
Prof Erica Wood	Co-director, Division of Acute & Critical Care, School of Public Health & Preventive Medicine, Monash University Consultant clinical and laboratory haematologist at Monash Health

Prof Zoe McQuilten	Consultant Haematologist, Monash Health Deputy-director Transfusion Research Unit, Monash University
Prof Craig French	Director of Intensive Care, Western Health Clinical Professor, The University of Melbourne
Prof Edward Litton	Senior Staff Specialist and Director of Research, Intensive Care Unit, Fiona Stanley Hospital, Perth, Western Australia
Prof Claire Rickard	Professor of Infection Prevention and Vascular Access at University of Queensland and Herston Infectious Diseases Institute (Metro North Health)
Dr James Daly	Medical Director Pathology Services, Australian Red Cross Lifeblood
Dr Andrew Flint	Intensive Care Registrar, Intensive Care Services, Royal Brisbane and Women's Hospital, Brisbane
Dr Adam Irving	Research Fellow, Joint appointment across Monash University's Centre for Health Economics & Transfusion Research Unit
Prof Peter Watkinson	Professor of Intensive Care Medicine, University of Oxford, UK Consultant Intensive Care Physician, Oxford University Hospitals NHS Trust
Prof Simon Stanworth	Professor of Haematology and Transfusion Medicine, University of Oxford, UK Consultant Haematologist, NHSBT and Oxford University Hospitals NHS Trust
Ms Kate Wilson	Consumer representative, haematology
Ms Belinda Howe	Senior project manager, ANZIC Research Centre, School of Public Health & Preventive Medicine, Monash University
Mr Dale Trevor	Consumer representative, intensive care
Dr Lisa Higgins	Health Economics Senior Research Fellow, ANZIC-RC, Monash University

Dr Akshay Shah	Anaesthetist, NIHR Clinical Lecturer, University of Oxford
Dr Douglas Gould	Senior Researcher, Intensive Care National Audit & Research Centre
Ms Hayley Noble	UK Trial Manager, Intensive Care National Audit & Research Centre
Ms Daisy Lindsay	Research Coordinator, Department of Intensive Care Medicine, The Royal Brisbane and Women's Hospital, Qld, Australia

3.5 Trial Steering Committee

A Trial Steering Committee (TSC) has been established in line with the latest National Institute for Health Research (NIHR) guidelines (i.e. consist of 75% independent members – including the Chair). The TSC will be responsible for overall supervision of the international trial and will ensure that the trial is conducted in accordance with the rigorous standards set out in the UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The TSC comprises of the Chief Investigator, a senior representative from the Intensive Care National Audit & Research Centre (ICNARC) Clinical Trials Unit (CTU), independent members (including independent consumer representatives), and an independent Australian representative.

4 Australian Trial Management Group authorisation page

We, the management group, have read the attached protocol version 1.0, dated 5 March 2024, and authorise it as the official protocol for the study entitled "The Threshold for Platelets study: a prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure".

Dr Elissa Milford	_____	Date:_____
Prof Michael Reade	_____	Date:_____
Prof Erica Wood	_____	Date:_____
Prof Zoe McQuilten	_____	Date:_____
Prof Craig French	_____	Date:_____
Prof Edward Litton	_____	Date:_____
Prof Claire Rickard	_____	Date:_____
Dr James Daly	_____	Date:_____
Dr Andrew Flint	_____	Date:_____
Dr Adam Irving	_____	Date:_____
Prof Peter Watkinson	_____	Date:_____
Ms Kate Wilson	_____	Date:_____

Ms Belinda Howe _____ Date:_____

Mr Dale Trevor _____ Date:_____

5 Lay description

Platelets are a type of blood cell that help form blood clots and stop bleeding. Platelet transfusions are given when the number of platelets in the blood (the platelet count) falls below a critical level (the transfusion threshold). Platelet transfusions are commonly given to critically ill patients as these patients often have fewer platelets in their blood than healthy people. A common reason to give a platelet transfusion to a critically ill patient with low platelet levels is to reduce the risk of bleeding before undergoing an invasive procedure.

However, platelet transfusions may have risks, such as an allergic reaction, and may not work as well in critically ill patients. We do not know to what level the platelet count should fall (the best transfusion threshold) before the benefits of giving platelet transfusions outweigh the risks. Given this uncertainty, a wide range of transfusion thresholds are currently used in intensive care units (ICUs) around the world to decide when a platelet transfusion should be given before undergoing an invasive procedure.

This study is a large international clinical trial to find out the best transfusion threshold below which a platelet transfusion should be given to patients who need an invasive procedure in ICU. The study will include 2,550 patients worldwide. Patients will be randomly allocated (by chance) to one of five platelet transfusion thresholds. If a participating patient's platelet count drops below their allocated threshold, they will be given a platelet transfusion before their procedure. We will follow up all patients at 90 days and one year. We will work out the best transfusion threshold by comparing the number of patients alive in each group at 90 days.

6 Background and rationale

6.1 Introduction

T4P is a United Kingdom (UK)-led, investigator-initiated, multi-centre, novel, Bayesian adaptive randomised controlled trial in 2,550 critically ill patients worldwide. It will provide the first high quality evidence of the optimum platelet threshold below which platelets should be transfused prior to an invasive procedure in ICU patients and will explore whether the optimum threshold differs according to patient characteristics.

T4P commenced recruitment in the UK in September 2022 with a target of 66 UK sites. Recruitment in Australia will commence in 2024 with a recruitment target of 500 patients across approximately 20 Australian ICUs. The Australian trial is supported by a Medical Research Future Fund (MRFF) International Clinical Trials Collaboration grant. T4P in Australia will be sponsored and coordinated by The University of Queensland and is supported by the Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG), the Blood Synergy Investigators, and the Australian Red Cross Lifeblood.

There is a long history of successful collaboration between UK and Australian researchers in transfusion medicine, including the randomised Trial of Prophylactic Platelets Study (TOPPS) in haematological malignancies, the REDDS programme of red cell transfusion support in myelodysplastic syndrome, and a Trial to Evaluate Tranexamic Acid Therapy in Thrombocytopenia (TREATT)[2-5].

6.2 Summary of the evidence

6.2.1 Platelets are a scarce resource and are frequently transfused in ICU

Severe thrombocytopenia (platelet count <50 x 10^9/L) occurs in approximately 12% of ICU patients[6], and approximately 5-10% of ICU patients receive a platelet transfusion during their admission in Australia and the UK[6-8]. Most of these transfusions are given prophylactically with the goal of preventing spontaneous or procedure-induced bleeding in patients with thrombocytopenia[6,8]. After cancer services, ICUs have the highest usage rates of prophylactic platelet transfusions[9,10]**.** Approximately 124,000 units of platelets are issued annually in Australia by the Australian Red Cross Lifeblood[11] at an estimated annual cost of over $40 million[12], not including unquantified administration costs.

Platelets are a scarce resource, donated altruistically by the community, with a short shelf-life of up to 7 days in Australia. Maintaining an adequate inventory is challenging due to increasing demand[13], and as a consequence of the effects of COVID19 pandemic[14-17]. Therefore, it is important that donated platelets are used appropriately to give the best outcomes for patients and donors. This has been identified as a high research priority by Australian and international blood policy and transfusion practice[10,18,19].

6.2.2 Platelet transfusions are associated with risks

Platelet transfusions are independently associated with an increased risk of lung injury, infection, transfusion reactions (highest rate of any blood component) and alloimmunisation, prolonged ICU and hospital length of stay, and mortality[7,20,21]. Causality is biologically plausible as platelets mediate multiple physiological processes beyond clotting, including interactions with immunological pathways. The systemic inflammatory state of critical illness may predispose, or prime, the immune, endothelial, and coagulation systems, to complications from platelet transfusions[20], meaning the ICU population may be more vulnerable to the risks of platelet transfusions than other patient groups.

6.2.3 The evidence to support platelet transfusion in ICU is limited

Clinicians primarily use a low platelet count to decide whether to give a platelet transfusion[22]. However, despite their common use, it is unclear whether platelet transfusions reduce bleeding in critically ill patients, and if they do at what platelet count transfusion threshold the benefits outweigh the risks of harm. Until recently, the literature on this topic consisted of retrospective cohort studies and two small single centre clinical trials. These studies have many limitations, conflicting conclusions, and by design, are not of a sufficient grade of evidence to inform clinical practice[23-28]. An updated exploratory meta-analysis which collated data across all trials in different clinical settings found no evidence of an effect of platelet transfusions on reducing bleeding or all-cause mortality[20], but recognised the lack of data in critical illness In some trial settings there was not only no evidence of a benefit of platelet transfusions on reducing major bleeding or mortality, but signals of harm, for example in critically ill pre-term neonates[20].

A recently published, multi-centre, randomised, controlled, non-inferiority trial enrolled 338 patients on the haematology ward or in critical care, with platelet counts of 10-50 x 10^9/L undergoing insertion of a central venous catheter (CVC) (the PACER trial)[29]. The authors concluded that withholding a platelet transfusion by adopting a restrictive transfusion policy was associated with more bleeding than platelet transfusion. However, bleeding occurred predominantly in haematology ward patients undergoing subclavian CVC insertion, which is not a common insertion site in many countries or settings[30]. The risk of bleeding and the efficacy and risk of harms of platelet transfusion in the two patient populations of haematology and critical illness are likely to be different due to differences in the causes of thrombocytopaenia, , and the degree of systemic inflammation[6,31,32]. This may explain why in the small ICU subgroup, there was no significant reduction in bleeding risk following platelet transfusion. There was also no significant increase in bleeding risk in the severe thrombocytopaenia subgroup (platelet count 10-19 x 10^9/L) without platelet transfusion, which is inconsistent with the hypothesis that low platelet counts are associated with an increase in bleeding risk.

The primary outcome in the PACER trial was bleeding, and many of the bleeding episodes were Grade 2, often only requiring manual compression. The patient-centeredness of this outcome is questionable, and it only assesses the benefits of a platelet transfusion and does not assess the effect of harms. The ICU subgroup in the PACER trial experienced trends that did not reach the predefined threshold for statistical significance (in this small cohort) for greater incidence of acute lung injury, longer ICU length of stay, and greater mortality, as well as two transfusion reactions to platelets. These outcomes may be more important to patients than non-severe bleeding. By using all-cause mortality as its primary outcome, T4P will measure the combined effect of benefits and harms in ICU patients.

The PACER trial, as all threshold randomised trials of platelet transfusions, was a traditional two-arm trial design, and could only compare the benefits of giving or not giving a platelet transfusion at two, possibly arbitrary, thresholds Two arm trial designs like this, which compare two maximally separated platelet count thresholds below which platelets are transfused (for example 20 versus 50 x 10^9/L), are unlikely to identify optimal thresholds. To establish the platelet threshold below which platelet transfusion confers a cost-effective patient benefit, T4P uses a novel, randomised adaptive comparative effectiveness design allowing simultaneous study of multiple platelet thresholds to define the optimum threshold by modelling a threshold-response curve.

The uncertainty of when pre-procedure prophylactic platelet transfusions confer benefit over harm has led to variation in clinical practice and guidelines in Australia and globally which may be

resulting in unmeasured harm[10,20,22,33]. The range of platelet counts over which platelet transfusions are given to critically ill patients prior to a low bleeding risk invasive procedure is wide, although the majority occur in patients with a platelet count in the range < 10-50 x 10^9/L[6,8,33-35].

6.3 Expected outcomes of the trial

T4P will provide the first and highest-quality evidence of the clinical and economic effectiveness to support a decision on when a pre-procedural, prophylactic platelet transfusion should be administered in ICUs in Australia and internationally. Contributing Australian patients to this international clinical trial will increase the generalisability of the trial results to Australian patients and result in faster translation of the results into clinical practice in Australia. Australia and the UK have a similar approach to platelet transfusion practice. Guidelines for platelet transfusion and specifications by platelet count content are comparable between the two countries. All platelet components, whether apheresis or buffy-coat derived, are leucoreduced, and common practice is to transfuse ABO and RhD identical platelets. Australian participation in the trial will also allow for an economic evaluation from the perspective of the Australian healthcare system, as well as enhance Australian clinical trial infrastructure and capacity. Ultimately, T4P will inform policy and clinical practice to improve outcomes for patients and to ensure the most effective and efficient use of donated platelets.

7 Study design

7.1 Aim

To define the optimum platelet threshold below which platelets should be transfused prior to an invasive procedure in critically ill patients (Figure 1), and to explore whether the optimum threshold differs according to patient characteristics.

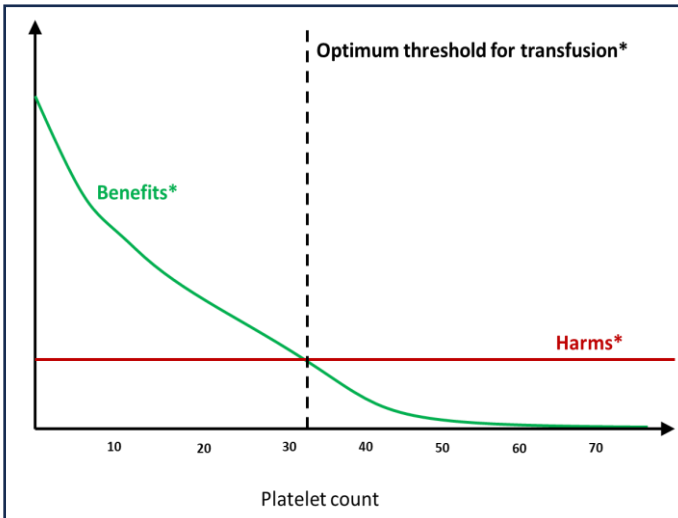


Figure 1. Illustrative optimum platelet count threshold for a hypothetical* combination of benefits and harms.

7.2 Hypothesis

That platelet transfusion in critically ill patients has net clinical and monetary benefit only below certain thresholds where any gain of preventing bleeding exceeds harm from exacerbating inflammatory and/or infective processes.

7.3 Objectives

- To model the threshold-response curve for the effect of platelet transfusion prior to/during an invasive procedure in critically ill patients (Figure 2 and in the Simulations Appendix at https://www.icnarc.org/Our-Research/Studies/Current-Studies/T4P/About).
- To evaluate whether the optimum value of the threshold-response curve varies according to patient characteristics.
- To evaluate the cost-effectiveness of standardisation of practice to the optimum threshold versus current usual practice, including an Australian economic evaluation.

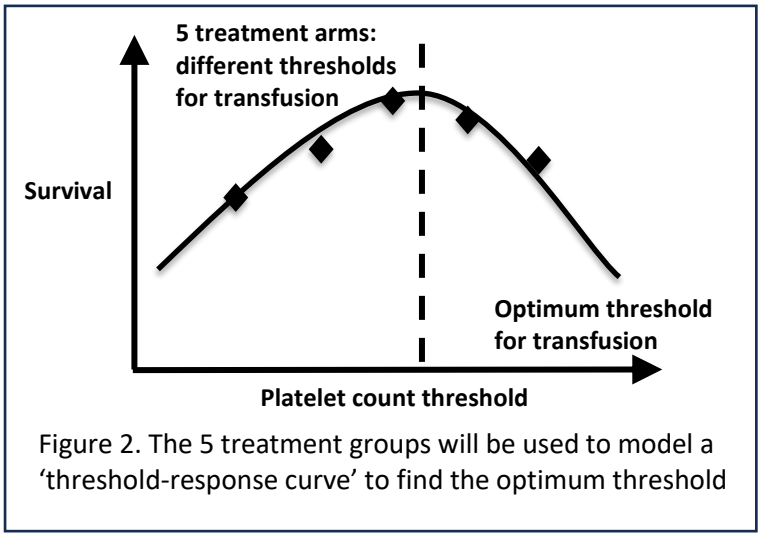


Figure 2. The 5 treatment groups will be used to model a 'threshold-response curve' to find the optimum threshold

7.4 Study design

Open label, randomised, Bayesian adaptive comparative effectiveness trial across five equally spaced thresholds of thrombocytopenia (<10 – <50 x 10^9/L).

7.5 Primary outcomes

- Clinical effectiveness: All-cause mortality at 90 days.
- Cost-effectiveness: Incremental costs, QALYs and net monetary benefit at 90 days.

7.6 Secondary outcomes

- Mortality at discharge from ICU, hospital and at one year
- Survival to longest available follow-up
- Rates of major and fatal bleeds classified according to the HEmorhage MEasurement (HEME) bleeding score[1]
- Venous and arterial thromboses in hospital and to one year
- Duration of renal, advanced cardiovascular and advanced respiratory support according to UK Critical Care Minimum Data Set (CCMDS) criteria
- Length of critical care unit and acute hospital stay
- Health-related quality of life (EQ-5D-5L questionnaire at 90 days and one year)
- Resource use and costs at 90 days and one year
- Net monetary benefit at one year

7.7 Australian sites

Just under 20% (around 500 patients) of the total study participants will be recruited from approximately 20 Australian ICUs over 3 years. Study interventions will occur in the admitting ICU, or where in the hospital the procedure takes place if it precedes an ICU admission.

7.7.1 Australian site requirements

- Compliance with all responsibilities as stated in the T4P Clinical Trial Research Agreement
- Compliance with all requirements of the Australian trial protocol
- Compliance with the principles of Good Clinical Practice (GCP)

7.7.2 Australian site responsibilities

- Identify a Principal Investigator (PI) to lead the T4P trial locally
- If possible, appoint an Associate/Sub PI to assist with the running of the T4P trial locally
- Identify a T4P research coordinator responsible for day-to-day local trial coordination
- Agree to incorporate T4P into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation
- Agree to adhere to individual patient randomisation allocations (unless safety concerns) and ensure adherence with the trial protocol
- Agree to aim to randomise all eligible patients at the time of decision to admit to ICU and to maintain a Screening Log
- Agree to train all staff who undertake low bleeding risk procedures to randomise patients into the trial
- Agree to data collection requirements

7.7.3 Australian site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- A completed site initiation visit (held in person or virtually)
- All relevant institutional approvals (e.g. site research governance authorisation)
- A fully signed T4P Clinical Trial Site Agreement

- A completed Delegation Log

Once the Australian coordinating centre has confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the Principal Investigator (PI), at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- Adherence with the most recent approved version of the trial protocol
- Training of relevant site staff in accordance with the trial protocol and GCP requirements
- Appropriate means to identify and randomise eligible patients into the trial
- Timely data collection, entry, and validation
- Prompt notification of all serious adverse events (SAEs)

All local staff (i.e., PI, Associate/Sub PI, local investigators, research teams) involved in the conduct of the trial must be trained to carry out their assigned roles. Site research staff should be signed off by the PI on the Delegation Log, once trained, and the Delegation Log copied and sent to the Australian coordinating centre whenever changes are made.

Staff members solely involved in the screening and randomisation of patients should be provided with trial-specific training to carry out these tasks and recorded on the Training Log (full GCP training will not be required for these staff members).

7.8 Participants

Critically ill adults admitted to, or requiring admission to, an ICU who have low platelet counts (< 50 x 10^9/L) prior to an invasive procedure of low bleeding risk.

To be eligible for the T4P Trial, patients must meet all the inclusion criteria, and none of the exclusion criteria **at the time of randomisation**:

7.8.1 Inclusion criteria

1. Adult (aged ≥ 18 years)
2. Accepted for admission or admitted to a participating ICU
3. Platelet count < 50 x 10^9/L
4. Planned to undergo a **specified** low bleeding risk invasive procedure OR platelet transfusion considered for an **'other'** low bleeding risk procedure

Specified low bleeding risk invasive procedures include the following:

- CVC insertion (including vascular access for renal replacement therapy)
- Paracentesis/superficial abdominal fluid collection drainage
- Pleural aspiration

'Other' procedures may be included if the clinician deems these to be a low bleeding risk invasive procedure and a platelet transfusion is being considered for the procedure. These include, but are not limited to:

- Arterial catheter insertion
- Arterial or central venous catheter removal
- Pleural drain
- Interventional radiology

- Bronchoscopy with or without lavage
- Wound dressing changes
- Surgical procedures where the clinical team agree risk of bleeding is low, e.g. re-look laparotomy, or wound closure

7.8.2 Exclusion criteria

1. Ongoing major haemorrhage requiring blood products and/or surgical/radiological intervention†
2. Intracranial haemorrhage within prior 72 hours†
3. Contra-indication to platelet transfusion (such as thrombotic microangiopathies; heparin-induced thrombocytopenia; immune thrombocytopenia; congenital platelet function defects)
4. Acute promyelocytic leukaemia (APML)
5. Known advance decision refusing blood/blood component transfusions (e.g. Jehovah's Witnesses)
6. Death perceived as imminent or admission for palliation
7. Previously randomised into T4P
8. Fulfilled all the inclusion criteria and none of the other exclusion criteria ≥ 72 hours

†Exclusion criteria 1 and 2 are dynamic, if resolved, the patient may be reconsidered for the trial.

Patients undergoing procedures not eligible for randomisation will remain available for inclusion where subsequent eligible procedures occur.

7.9 Co-enrolment

Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed.

The T4P investigators will consider co-enrolment of participants into other interventional studies where there is no possible conflict with the T4P objectives. Co-enrolment agreements will be put in place on a trial-by-trial basis.

8 Study procedures

8.1 Screening

At the point of the decision to admit to an ICU, potentially eligible patients will be screened against the inclusion and exclusion criteria by the local clinical team, supported by the site research team. Screening Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

Once admitted to an ICU, patients with platelet counts $\geq 50 \times 10^9$/L will be screened daily until recruitment, refusal, or ICU discharge. Once a patient first meets all inclusion criteria and none of the exclusion criteria, they should be randomised within 72 hours.

8.2 Randomisation

Randomisation will occur as soon as possible (< 72 hours) after confirming eligibility. Randomisation will be performed by the site investigator, research coordinator or delegated staff at each site. Patients will be randomised to one of five platelet thresholds using a central web-based randomisation service, available 24 hours/seven days per week.

Following randomisation into T4P, each participant will be assigned a unique T4P Trial Number and a case report form (CRF) will be completed by the local team.

Enrolment in the study must be documented in the participant's medical record in accordance with local policy and practices.

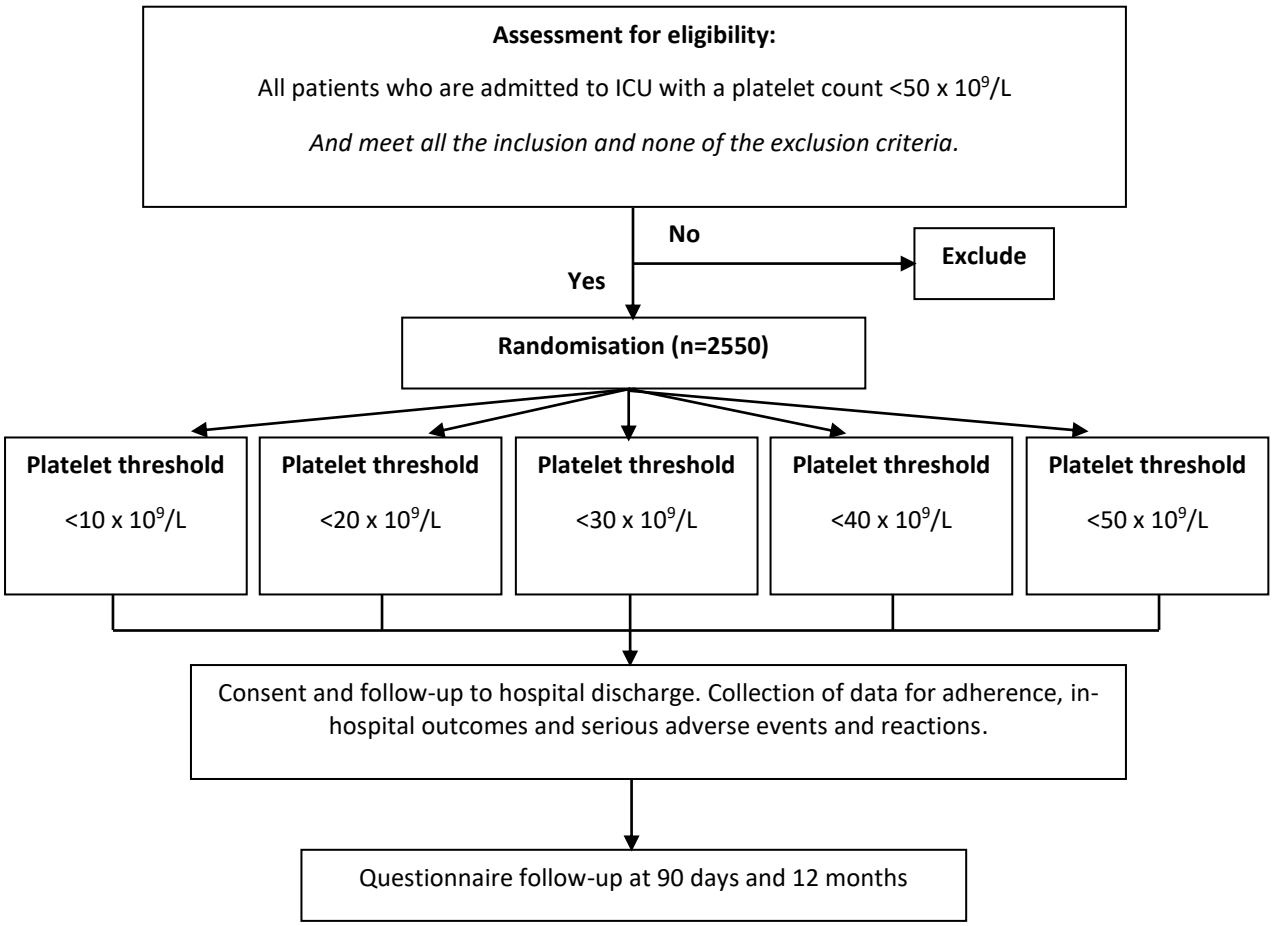
8.3 Interventions

Patients will be randomised to one of five equally spaced platelet thresholds (<10 - <50 x 10^9/L) (Figure 3), below which they would receive a single adult equivalent dose (AED, defined according to national specifications) of platelet transfusion delivered before or during the procedure.

Treatment according to the randomly allocated threshold will continue for all subsequent low bleeding risk invasive procedures until ICU discharge (i.e. all low bleeding risk procedures for which the patient's most recent platelet count is below the allocated threshold). If a patient is readmitted to an ICU during the index hospital stay within the 90 days, treatment according to the randomly allocated threshold will be recommenced. Procedures occurring after ICU discharge are at discretion of the clinical team and do not need to follow the allocated treatment threshold.

Randomisation and group allocation are independent of baseline platelet count. The treating clinician will be notified of group allocation immediately following randomisation so they can determine whether the participant should or should not receive a pre-procedure platelet transfusion on the initial and subsequent occasions. For example, if a participant is randomised to the <30 x 10^9/L group, the randomisation notification will tell the treating clinician: "The threshold for platelet transfusion is: Less than 30 x 10^9/L". If the participant's initial platelet count is 19 x 10^9/L, then they should be given a single unit platelet transfusion before the first procedure (the procedure that determined eligibility for the trial) and for any subsequent procedure where their platelet count is <30 x 10^9/L. If the participant's platelet count is above 30 x 10^9/L prior to a subsequent low bleeding risk procedure, then they should not receive a transfusion. There is no requirement to recheck the platelet count following the pre-procedure platelet transfusion.

Figure 3. Trial flow chart



8.4 Co-interventions

All other care will be provided at the discretion of the treating clinical team.

Where a patient is receiving a low bleeding risk invasive procedure, platelet prophylaxis is only permitted according to allocated randomised threshold. Where significant bleeding occurs during or after a low bleeding risk invasive procedure, or where platelets are given outside of any procedure, platelet administration should follow local guidance. Platelets are permitted for high bleeding risk interventional procedures.

8.5 Monitoring adherence to the intervention

Adherence to the trial protocol will be assessed by comparing, for each threshold, both the proportion of patients who crossed their assigned threshold prior to a planned procedure and (correctly) received a platelet transfusion before the procedure, and the proportion who did not cross their threshold prior to a planned procedure and (correctly) did not receive a transfusion before the procedure. Adherence will be assessed separately with respect to each patient's first procedure and any subsequent procedures.

Protocol non-adherence will be defined as:

- Receipt of platelet transfusion for low bleeding risk procedure when platelet count is above randomly allocated threshold
- Platelet transfusion not received for low bleeding risk procedure when platelet is below randomly allocated threshold

8.6 Modifications to the protocol

This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document or consent documentation that affects the scientific intent, study design, patient safety, or may affect a participant's willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or consent documentation. All such amendments will be submitted to the HREC, for approval prior to becoming effective.

9 Safety monitoring and reporting

9.1 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC has been set up to monitor recruitment and retention, protocol adherence (including adherence to treatment protocols) and patient safety. The DMEC will receive and review the progress and accruing data and provide advice on trial conduct to the TSC. The DMEC will also review the results of planned adaptive analyses to ensure that the pre-specified trial algorithm is being implemented as designed, and that the design remains appropriate from a scientific and ethical standpoint. The DMEC is also responsible for the review of unblinded safety data and will be notified of unexpected and serious adverse events and will make recommendations to the TSC of any action required.

9.2 Definitions

The following definitions have been adapted from Directive 2001/20/EC of the European Parliament (Clinical Trials Directive) and ICH-GCP guidelines (E6(R1), 1996).

Adverse Event

An Adverse Event (AE) is defined as: any untoward medical occurrence or effect in a patient participating in a trial.

Serious Adverse Event

An adverse event is defined as serious if it:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

"Life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

"Hospitalisation" refers to inpatient admission, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

9.3 Assessment

The site PI, or other medically qualified investigator as listed on the Delegation Log, should make an assessment of the severity, relatedness and expectedness, categorised as follows:

9.3.1 Severity

- None: indicates no event or complication
- Mild: complications result in only temporary harm and do not require clinical treatment
- Moderate: complications require clinical treatment but do not result in prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitations to the patient
- Severe: complications require clinical treatment and results in prolongation of hospital stay and/or permanent functional limitation
- Life-threatening: complication that may lead to death
- Fatal: where the participant died as a direct result of the complication/adverse event

An event assessed as 'Severe', 'Life-threatening' or 'Fatal' will be considered a Serious Adverse Event (SAE).

9.3.2 Relatedness

- None: there is no evidence of any relationship to the trial treatment
- Unlikely: there is little evidence to suggest a relationship to the trial treatment, and there is another reasonable explanation of the event
- Possibly: there is some evidence to suggest a relationship to the trial treatment, although the influence of other factors may have contributed to the event
- Probably: there is probable evidence to suggest a relationship to the trial treatment, and the influence of other factors is unlikely
- Definitely: there is clear evidence to suggest a relationship to the trial treatment, and other possible contributing factors can be ruled out

9.3.3 Expectedness

- Expected: the event is a pre-defined expected SAE event for this trial.
- Unexpected: the event is not a pre-defined expected SAE event for this trial

Pre-defined expected SAEs for T4P that could be observed in participants up to ICU discharge following randomisation are:

- Major and fatal bleeds classified according to the HEME bleeding score
- Serious transfusion related adverse reactions which relate to the administration of the platelet transfusion

9.4 Recording and reporting procedures

Occurrences of the specified, expected Serious Adverse Events (SAEs) will be recorded and reported for all randomised patients from the time of randomisation until ICU discharge. If a patient is readmitted to the ICU during the index hospital stay within the 90 days, safety monitoring will be recommenced.

Considering that all eligible patients are critically ill and at increased risk of experiencing multiple adverse events due to the complexity and severity of their condition – occurrences of non-specified, unexpected, SAEs will only be reported if they are considered to have possibly, probably, or definitely (as per section 9.3.2) occurred as a consequence of receiving or not receiving a platelet transfusion for a low risk invasive procedure (i.e. not events that are part of the natural history of the primary disease process or expected complications of critical illness). Note that death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness as detailed above.

All SAEs (other than those defined in the protocol as not requiring reporting) must be recorded in the patients' medical notes and reported to the Australian and central (international) coordinating centre via completion of the SAE Report eCRF on the secure electronic data entry system, **within 24 hours** of observing or learning of the SAE(s). The completed SAE Report Form should be electronically signed off by the site PI (or medically qualified delegate). An email notifying the trial team of completion of the SAE Report Form should be sent to T4P@icnarc.org AND AusT4P@uq.edu.au. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available. If the eCRF is unavailable, the SAE report can be completed on paper and a scanned copy sent by email to T4P@icnarc.org AND AusT4P@uq.edu.au.

On receipt of an SAE report, a member of the central (international) coordinating centre will first evaluate the report for completeness and internal consistency. Then, a clinical member of the central T4P Trial Management Group will evaluate the event for severity, relatedness and expectedness and liaise with the Australian Trial Management Group to determine whether the case qualifies for reporting to the (Australian) HREC and any further actions required, in accordance with local jurisdictional requirements and policy directives.

All other adverse events that occur between randomisation and 90 days post-randomisation (or ICU discharge, if sooner) must be recorded in the participant's medical notes.

The coordinating (international) centre will provide safety information to the DMEC on a basis deemed appropriate by the DMEC.

9.5 SUSARs

A SAE whose nature, severity, specificity, or outcome is not consistent with the expected complications of the intervention will be considered 'unexpected'. A SAE which is both unexpected and has a causal relationship with the study intervention will be reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR) by the Australian Coordinating Centre to the TGA in an expediated fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life-threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. An investigator will complete, sign and submit the SUSAR report. These reports will then be forwarded to all sites for reporting to their HRECs as required.

9.6 Statutory reporting

All suspected transfusion reactions should also be reported as per local transfusion reaction reporting standard procedures.

10 Statistical and data analysis

10.1 Sample size

Sample size was estimated from simulations across 7 hypothesised threshold-response curves for the 90-day mortality primary outcome. These simulations are available in the simulations appendix at https://www.icnarc.org/Our-Research/Studies/Current-Studies/T4P/About. A sample size of 2400 resulted in power of at least 92% across the different scenarios to recommend an optimum threshold with a true mortality within 2% (in absolute value) of the optimum mortality value (Table 2, simulation appendix). The sample size was increased to 2550 patients to allow for 6% refusal/withdrawal of consent post-randomisation (as in the "65" Trial[36]).

10.2 Australian sample size

An Australian sample size of 500 was chosen as this is a large enough cohort to complete an Australian economic evaluation and to increase the generalisability of the trial results to Australian patients. This figure is also feasible within the trial period and will coincide with the projected completion of recruitment in the UK (August 2027) and Australia within 3 years of Australian recruitment commencement.

Over a recent 12-month period at three tertiary and one regional ICU in South-East Queensland there were approximately 3.4 patients per site-month in the tertiary centres and 0.75 patients per month in the regional centre that met the inclusion criteria. Allowing for a recruitment rate of one in three eligible patients and a recruitment period of nearly three years, approximately 13 tertiary sized centres would be needed to recruit the target of 500 patients. To allow for smaller centres, a site ramp-up period of 6 months, and a lower than predicted recruitment rate, 20 Australian ICUs as Australian study sites will be recruited.

10.3 Clinical effectiveness analysis

All analyses will be pre-specified in a Statistical Analysis Plan published prior to the first interim analysis. Reporting will follow CONSORT guidance[37]. Primary analyses will be on an intention-to-treat basis. Baseline patient characteristics will be compared across thresholds to assess the effectiveness of randomisation at achieving covariate balance.

The threshold-response curve for each outcome will be fitted using fractional polynomials of order 2 to estimate a continuous non-linear relationship between the allocated threshold and the outcome[38]. Model uncertainty will be taken into account using Bayesian model averaging. The estimand of interest is the threshold leading to the maximum probability of survival. Binary outcomes (including the primary outcome) will be modelled using logistic regression, continuous outcomes using linear regression.

Regression models will be adjusted for stratification variables (random effect of site) and other pre-specified patient factors with an established relationship with outcome among critically ill patients. These patient factors will be agreed with the Trial Steering Committee and prespecified in the Statistical Analysis Plan (SAP). As a sensitivity analysis for the primary outcome, the threshold-response curve will be fitted using a Gaussian process model.

The primary output will be a set of statistics derived from the estimated threshold response curve, including the location of the optimum, reported with a 95% credible interval and estimates of the probability of survival at all thresholds across the full range of investigated thresholds, each with a corresponding 95% credible interval. If the estimated threshold-survival curve is relatively flat (i.e. there are only small differences in mortality across the range) then the location of the optimum will

be less certain (i.e. have a wider credible interval) but any error in locating the optimum will also be less important. Both the shape of the curve and the location of the optimum are therefore of clinical interest. A steep curve would imply a narrow region within which clinical judgement should be exercised, and a flatter curve would support a wider region. Examples of potential outputs are provided in the simulation study report (see simulation results in the appendix found online https://www.icnarc.org/Our-Research/Studies/Current-studies/T4P/About).

Variation in the threshold-response curve shape and optimum threshold location in pre-defined patient subgroups will be evaluated by introducing interaction terms between the subgroups and the threshold in the threshold-response models for the primary outcome.

We will handle missing data appropriately within the Bayesian paradigm, adding imputation sub-models for missing covariates if required. Assumptions about the missing values will be fully specified in the SAP.

Analyses of long-term outcomes involving data linkage to efficiently collect follow-up data are potentially subject to influence of linkage error (missed links between one patient's records or false links between different patients). With collection of multiple, highly specific patient identifiers (e.g. hospital number, postcode and date of birth), false links are expected to be negligible but will be assessed by checking linked records for implausible scenarios such as activity after death. Missed links due to incomplete or inaccurate recording of identifiers (especially in any of the linked datasets) are a common issue in studies of linked data and can lead to missing data and/or misclassification of outcomes. The risk of missed links will be minimised by collection of multiple patient identifiers and the potential influence will be assessed by comparing the completeness and validity of available identifiers, and match rates for linkage to core datasets across treatment groups. Where matching data are insufficient or where linkage has been unsuccessful to core datasets, all outcomes derived from linked data for that patient will be treated as missing.

10.4 Subgroup analysis

Planned pre-determined analyses, where numbers are sufficient, of patient groups with:

- Underlying bone marrow failure (defined as a white cell count $<1.0 \times 10^9$/L with an explanatory underlying diagnosis, e.g. haematological malignancy, receiving chemotherapy)
- Underlying liver disease (defined as acute hepatic failure as primary reason for ICU admission or severe chronic liver disease - biopsy proven cirrhosis, portal hypertension or hepatic encephalopathy)
- Sepsis (defined according to Sepsis-3 criteria[39])

10.5 Interim analysis

There will be three interim analyses following the recruitment and follow-up to 90 days of 830, 1340 and 1850 patients. Interim analyses will include preliminary modelling of the threshold-survival curve to inform adaptation of the allocation ratio based on the probabilities that each modelled threshold has the highest survival percentage. Up to two outer thresholds (potentially at the same end of the spectrum) will be dropped if their posterior probability of having the highest survival percentage is less than 1%. All remaining thresholds will always have a minimum allocation percentage of 5%. Allowing for recruitment during the 90-day follow-up, the adapted randomisation ratios are anticipated to take effect after the recruitment of 1020, 1530 and 2040 patients.

10.6 Stopping rules

There will be no formal statistical rules for stopping for efficacy or futility, but the outer thresholds may be discontinued following planned interim analysis. However, the trial could be stopped if the DMEC raises concerns about harms.

10.7 Health economic evaluation

Within-trial (1 year) and modelled cost-effectiveness analyses (CEAs) will be undertaken. The CEAs will take a healthcare perspective, capturing resource use associated with delivering the intervention, hospital, and ICU length of stay (weighted by number of organ supports required), and the use of personal health services. The use of hospital outpatient visits and community services following discharge from the index admission will be collected via a health service questionnaire sent to patients at 90 days and 1-year post-randomisation and via linkage to the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) datasets. At the same time, patients will be asked to complete the EQ-5D-5L questionnaire to capture health-related QoL (HRQoL). Survival status at 90 days and 1 year following randomisation will be obtained via participating sites and/or data linkage with the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD).

Quality-adjusted life-years (QALYs) at 90 days and 1-year post-randomisation will be calculated by valuing each patient's survival time by their HRQoL according to the area under the curve approach. Unit costs for included resources will be obtained from national sources, and we will use bivariate regression models to allow for correlation between costs and QALYs, adjusting for the same baseline covariates as the clinical analysis. We will estimate cost-effectiveness for the same subgroups as for the clinical analysis and to inform the possibility of recommending different thresholds for platelet transfusion according to patient subgroup.

As the trial has more than two arms the CEAs will be summarised by a net monetary benefit (NMB) threshold-response curve over the time horizon, assuming a $50,000/QALY willingness-to-pay threshold. We will use long-term ICU survival data to extrapolate the results of the 1-year within-trial CEA to a lifetime time horizon for the modelled CEA. We will perform probabilistic sensitivity analysis by bootstrapping our sample of patients with replacement stratified by treatment arm to characterise the uncertainty in the NMB.

11 Ethics

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) E6 R2, NHMRC National Statement on Ethical Conduct in Research Involving Humans (2023)[40].

11.1 Ethics committee & research governance approval

The Australian coordinating centre will submit this protocol and any other relevant study documentation to the HREC. Sites will submit to their research governance office for local authorisation. It is the site PI's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC (or equivalent) as required by that committee. The inclusion in the trial of adults with incapacity to consent will be governed in accordance with the legal jurisdiction of each participating site.

11.2 Ethical considerations of the study

The ethical considerations of this study are:

• The risk/benefit ratio of the study treatment

• Data protection and confidentiality of participant data

• The enrolment of participants who are unable to consent for themselves

11.2.1 The risk/benefit ratio of the trial's comparison of standard care treatment arms

The range of platelet counts over which platelet transfusions are given to critically ill patients prior to a low bleeding risk invasive procedure is wide, with the majority occurring in patients with a platelet count in the range < 10-50 x 10^9/L[6,8,33-35]. The five transfusion threshold arms of this trial encompass this range of usual care, and this trial is therefore comparing the effectiveness of these five strategies accepted by substantial numbers of medical practitioners specialising in the area of practice concerned. Participants in all arms of the trial will therefore be receiving treatment within the bounds of accepted standard clinical practice with no components of care being new or experimental. The treating clinician is expected to have equipoise about which of the five treatment strategies to employ in order to enrol a participant into the trial. Regardless of the treatment arm, and, because the trial is unblinded, the treating doctor retains ultimate control over whether the patient receives a platelet transfusion or not. The treating doctor may deviate from the treatment protocol if deemed to be in the interest of the participant (with the reasons for this documented in the CRF). Thus, participants in the trial are considered to be at no greater risk than if they were receiving treatment outside the trial. Thus, the risk/benefit ratio of the trial where both trial arms are encompassed by the range of usual care and is accepted as such by medical practitioners specialising in the area of emergency medicine and intensive care in Australia and New Zealand confers no greater clinical risk than receiving routine treatment.

11.2.2 Data protection and confidentiality of participant data

All investigators and research staff will comply with the legislative requirements of their jurisdiction with regard to the collection, storage, processing and disclosure of personal information. Confidentiality of all participant data will be maintained by the use of unique identifiers, password protected electronic databases, secure storage of records and precautions to control access to authorised personnel only. All records will be kept in compliance with local ethical and research governance policies.

Participants will be randomised via a secure database and allocated a unique study number. The site research coordinator will compile an enrolment log which contains identifying information. Subsequent data will be identified by the unique study number only. The enrolment log and study data will be kept separately. Follow-up details of the participant and their person responsible (if the participant has not regained adequate capacity) will be collected for the 90 day and 1 year outcome assessment conducted via telephone including name, address and contact telephone numbers/email. These contact details will be kept confidentially at the site in a locked filing cabinet in the site research office and will not be accessible outside the research team of the recruiting hospital.

11.2.3 The enrolment of participants who are unable to consent for themselves

Who may give consent for a patient to take part in medical research will vary between legal jurisdictions according to their local legislation. Each site's PI is responsible for ensuring that the relevant local legal requirements are followed. The term used to describe the person who may give

consent for a patient to take part in medical research will also vary between jurisdictions. For the purposes of this protocol, the descriptor 'person responsible' describes the person who is legally allowed to give consent for the participant.

All interaction between research staff and participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of a decision to participate. Consenting to participation will be voluntary and participants or their PR will be free to withdraw from participation at any time without giving reasons.

11.2.3.1 Urgent need for procedure and trial inclusion unable to be separated

Due to the critical nature of participant condition, the invasive procedure needs to occur rapidly often under emergency conditions and is part of being able to deliver life-saving care. Therefore, the study treatment arms, all which encompass standard care for patients with platelet counts of < 50 x 10^9/L requiring invasive procedures, cannot be separated from lifesaving care.

11.2.3.2 Unable to obtain patient or person responsible consent prior to enrolment

Time-critical invasive procedures often occur in the first hours of a critical care unit admission. Analysis of the Post-Intensive Care Risk-adjusted Alerting and Monitoring dataset[41] and the DRIVE (Desmopressin for procedures or Radiological InterVEntions) study dataset[42] shows that a large proportion of platelet transfusions occur on the first day in a critical care unit when critically ill patients commonly lack capacity. Both datasets also show platelet transfusion commonly occurs out-of-hours. The trial cannot delay these interventions but excluding these patients would impact upon the scientific validity. The emergency clinical situation and time-critical nature of invasive procedures can also cause profound distress for relatives, raising ethical concerns both about the burden of trying to understand the trial and the ability of the person responsible to provide an opinion about trial participation during a time of great distress, as recognised in section 4.4.11 of the National Statement[40]. In addition, delaying the clinical procedure while an urgent opinion from a person responsible is sought would not represent usual clinical practice and might delay essential treatment. For these reasons, attempts to obtain prior consent from a person responsible when the patient lacks capacity to consent, is inappropriate.

11.3 Waiver of consent for enrolment and consent for follow up

In view of the above, we will seek approval for enrolment without consent where this is consistent with local jurisdictional requirements and legislation. This approach is in line with the principles in paragraph 4.4.13 of the National Statement and is justified on the basis that the trial is comparing the effectiveness of five accepted treatment strategies and trial participation confers no greater clinical risk than receiving routine treatment, as detailed in protocol section 11.3. As reasonably practicable following recruitment, the PR and/or the participant will be informed of the participant's inclusion in the trial and consent for follow up sought.

Dependent on local jurisdictional requirements and legislation, consent for follow up at 90 days and 12 months will employ either one of the following two approaches:

- Opt-out
- Consent to continue

11.3.1 Consent for follow up using opt-out approach

Subject to local HREC approval and where opt-out approach to consent is consistent with local jurisdictional requirements and legislation, we will request an opt-out approach for follow-up at 90 days and 12 months following trial enrolment. We believe the conditions for this opt-out approach, as described in the National Statement 2.3.5 and 2.3.6[40] have been met in the T4P trial. Refer to Appendix 2 for the National Statement 2.3.6 opt-out approach criteria and the trial's specific meeting of these conditions. In our experience with trials in critically ill patients when approval for enrolment without prior consent has been granted, consumer representative advice is that participants and PRs often find it confusing to provide written consent for data when the research treatment procedures have already taken place and they frequently perceive that more research specific interventional procedures are required.

Where an opt-out approach is approved, the site PI, or their nominated delegate, will provide a plain language brochure to the participant and/or PR at the earliest opportunity. The brochure will explain the trial and the procedure to decline or opt-out from follow-up. Additional to this written information, the site PI, or their nominated delegate, will provide a verbal explanation of the trial and the opportunity to ask questions and have these answered. This combined process of both written information and verbal exchange will constitute an overall process to facilitate participant/PR understanding of the information. It will also provide the best opportunity for the participant/PR understanding of the information to be demonstrated to the research member undertaking the opt-out approach. This brochure will detail the process for declining or opting out of study participation. They will be given the brochure to keep and may seek further information or opt-out at any time. The provision of the opt-out brochure will be documented in the participants medical record and a copy of the brochure will be placed in the participants medical records. If the participant or PR decides to opt-out of the trial this will be clearly documented in the medical record.

11.3.2 Consent for follow up using consent to continue approach

Subject to local HREC approval, and where opt-out consent is not consistent with local jurisdictional requirements and legislation, we will seek consent to continue participation in the trial for the purposes of follow up at 90 days and 12 months. The site PI, or their nominated delegate, will provide a plain language information sheet and consent form to the participant and/or PR at the earliest appropriate opportunity. The information sheet will explain all aspects of the trial and the opportunity to ask questions and have these answered. This combined process of both written information and verbal exchange will constitute an overall process to facilitate participant/PR understanding of the information. It will also provide the best opportunity for the participant/PR understanding of the information to be demonstrated to the research member undertaking the consent to continue. They will be given the information and consent form to keep and may seek further information or withdraw at any time. The consent process will be documented in the medical record and a copy of the information and consent form will be placed in the participant's medical record.

11.3.3 Deceased patients

Participants enrolled in this study are critically ill and consequently the participant may deteriorate rapidly and unexpectedly. In the circumstance where a participant is enrolled in the study and dies before they are notified of their participation in the study, we will use participants' data for the study. All attempts to contact the family and relevant circumstances prior to the death of any participant will be documented in the medical record. To notify grieving family members of the

participants participation would be stressful and inappropriate. Additionally, the study integrity and safety data would be compromised without this data.

11.3.4 Informed consent to follow up cannot be obtained from the participant or person responsible

There may be the circumstance where a participant never regains competence following enrolment into the trial and there is no PR available. If the participant is under a Guardianship Order then consent to follow up will be sought following the legislation and processes in place in that jurisdiction as long as the Guardianship Order includes consent to medical treatment. In the circumstance of a participant who never gains capacity and there is no PR or a Guardianship Order which does not include decisions on consent to medical treatment, an approach will be made to the relevant HREC to request that study data may be retained and used.

11.3.5 Refusal or withdrawals of consent

If a participant or their PR chooses to opt out or declines consent to continue for follow up at any time during the trial, this decision will be respected and will be abided by. Participants or their PR will be free to withdraw from participation at any time without giving reasons. All data up to the point of this decision will be retained and included in the trial analysis, unless permission to all data is expressly refused, as the study integrity and safety data would be compromised without this data.

For patients or their PR who choose to opt out from follow up or decline consent to continue, but do not request removal of data, the site will enter minimal pseudonymised data required for the primary outcome – survival status (alive/dead) at 90 days after randomisation and date of death (where applicable) only. The justification for this is that as deceased patients cannot refuse consent to continue in the trial, excluding primary outcome data from the cohort of patients who survive to decline informed deferred consent would introduce substantial bias and may prevent evidence of significant clinical benefit from being detected. No patient identifiable data will be recorded and no further contact with the participant/PR about the trial will be required.

12 Data management

12.1 Data collection

Some data items will be collected by data linkage with the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD) and the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) dataset.

The remaining data items will be collected by trained research staff at each participating site. For these items, paper CRF worksheet may be used to collect the data from the medical record. Each participant will be assigned a unique study number at randomisation and only non-identifying data will then be entered into a web database (electronic case report form [eCRF]) by the site research staff. On all study-specific documents, other than the consent documents, the participant will be referred to by the study participant number/code, not by name.

12.2 Questionnaire follow-up

Each participant will be followed up with a questionnaire up to a maximum of one year. Participants or their PR will be asked to provide three possible points of contact (home and close family contact details) to the research staff prior to discharge. Participants (or a PR proxy) who are alive at 90 days and one year after randomisation will be contacted by the site research coordinator via telephone. If it is not possible to contact the participant or PR on the telephone, a copy of the relevant questionnaires will be sent to them via post or email, with a short text message follow up as a

gentle reminder. If the questionnaires are completed at home a return address, stamped-addressed envelope will be provided. The research coordinators will administer, or the participants or PR will complete, the EQ-5D-5L quality of life assessment and a health services questionnaire. These questionnaires are designed to take no longer than 15 minutes to complete.

If a patient is an in-patient at a participating site at either of the follow-up time-points, the site research team will approach the patient and conduct the questionnaire with them in hospital, if willing and if their condition permits. If a patient is on their initial acute hospital admission at either of the follow-up time points, they will not be asked to complete the health services questionnaire, as this contains only questions that are relevant following discharge from acute hospital.

12.3 Data variables collected

1. Screening
   - Patient identifier(s)
   - Inclusion and exclusion criteria
   - Reason for non-enrolment

2. Baseline (immediately prior to randomisation)
   - Baseline demographics
   - Severity of illness
   - Risk factors

3. Intervention
   - Data to monitor adherence with the protocol and randomised platelet transfusion threshold
   - Data on procedures undertaken, response to bleeding episodes and co-interventions

4. Outcome data
   - Secondary outcomes of ICU and acute hospital mortality
   - Organ support duration
   - Duration of ICU and acute hospital stay
   - Critical care costs from the index admission and any subsequent critical care readmissions
   - Date of deaths
   - Thromboembolism occurrence
   - Patient and PR contact details (to allow for questionnaire follow up)
   - Health care utilisation and quality of life outcomes up to one year post enrolment

5. Adverse event reporting
   - See section 9.

12.4 Data management

Direct access will be granted to authorised representatives from the Sponsor, the central and Australian coordinating centres and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution.

Security of the electronic data entry system is maintained through usernames and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act. ICNARC is registered under the UK Data Protection Act (Registration number: Z6289325). Data held by the Australian coordinating centre will be stored on the UQ Research Data Manager system in accordance with UQ data management principles.

All paper study records, including consent documentation, paper CRFs (if used) and electronic records will be kept securely and confidentially for 15 years following the completion of the study.

13 Quality assurance procedures

13.1 Risk Assessment

A risk assessment and monitoring plan for Australian sites will be prepared and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2 Study monitoring

13.2.1 Central monitoring

The central (international) and Australian coordinating centres will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of essential documents. Data will be actively and regularly reviewed centrally and site PIs will be contacted regularly to ensure protocol adherence and data quality are maintained.

13.2.2 Site monitoring

The on-site monitoring plan will follow a risk-based strategy. The timing and frequency of visits will be based on a risk assessment, including an assessment of each site's performance (including protocol adherence) and local research team (e.g. experience of conducting RCTs). A site initiation teleconference or visit will be conducted before site activation, and all sites will be visited at least once during the recruitment period to monitor and discuss adherence to the trial protocol and standard operating procedures. Following all site visits, a report will be sent to the site summarising the visit, documents reviewed and the findings. Learnings from site visits will refine the study procedures, as required, ensuring clarity and consistency across sites. Email and telephone communication will supplement site visits. In addition, remote videoconferencing facilities such as Zoom may be utilised as required.

Medical records, any other relevant source documents and the site investigator files must be made available to the study representative for these monitoring visits during the course of the study and at the completion of the study as needed.

The aims of monitoring visits are to:

- Check the accuracy of the data entered on the database by performing source data verification of the electronic CRF against the original source documents
- Check for protocol deviations and report these to the chief investigator as necessary
- Review primary and secondary outcome data available for each participant

- Confirm the consent procedures approved by the site's HREC have been followed and view each original signed consent form
- Check data security and access
- Review all serious adverse events (SAEs) and follow up all reported SAEs
- Review investigator site files for completeness and accuracy
- Assist the study staff with any queries or problems they may have in relation to the study

14 Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

All protocol deviations must be recorded in the patient record (source document) and on the CRF and must be reported to the site PI. Protocol deviations will be assessed for significance by the PI. Those deviations deemed to have a potential impact on the integrity of the study results, patient safety or ethical acceptability of the trial will be reported to the central (international) and Australian coordinating centres and HREC in a timely manner. Where deviations to the protocol identify issues for review, the protocol will be amended as required and approved by the HREC.

15 Funding

T4P recruitment in Australia is funded by an International Clinical Trial Collaborations grant from the Medical Research Future Fund (MRFF) (2031827).

16 Endorsement and partnership

T4P in Australia is conducted in partnership with the Blood Synergy group and the Australian Red Cross Lifeblood and is supported by the Australian and New Zealand Intensive Care Society Clinical Trials Group.

17 Pre-specified sub-studies

17.1 Epidemiology of central venous and peripheral arterial catheter complications in thrombocytopaenic ICU patients

In participants who undergo insertion or removal of a central venous or arterial catheter, the incidence, risk factors, and outcomes of bleeding, thrombosis, and other catheter related complications will be assessed. Further details of this sub-study are provided in the sub-study protocol.

18 Publications and reports

The first publication will be undertaken for overall analysis of the main trial using data from all participating countries. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge funding bodies in the publication. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

The results of the T4P trial will be disseminated actively and extensively. This will cover both progress during the trial period and the results at the end of the study. Outputs will include, but will not be limited to, the following areas:

- Annual newsletters and final results summary
- Webinars and recorded interviews with researchers, available through the trial website
- National and international conference presentations of study progress and results (with abstract publication)
- Prospective trial registration, with publication of study protocol and statistical analysis plan, for maximum transparency
- Publication of the primary results, and longer-term outcomes, including economic evaluation
- Publication of an analysis of our use of an adaptation of the recent MRC clinical trial unit 'Durations' design for modelling duration-response curves to evaluate minimum effective treatment durations within an adaptive trial design to support further use of these techniques for more efficient, informative threshold-based clinical trials in the future[38]
- Results synthesis to support incorporation into clinical guidelines
- Presentation slides and briefing papers for the study team to disseminate the research findings.

Articles will be prepared for publication in peer-reviewed scientific journals and in relevant professional journals. Outputs will be targeted at relevant stakeholders in formats suitable for the target audience to ensure that the potential benefit and impact of T4P are maximised.

19 Access to the final trial dataset

Once the data from the trial are fully analysed and published, the dataset will be made available in line with the National Institute for Health Research (NIHR) current recommendations.

20 Archiving

At the end of the trial, the ICNARC CTU will securely archive all necessary centrally held trial-related documents for a minimum of 5 years and primary/raw data for a minimum of 10 years, in accordance with GCP guidelines. Arrangements for confidential destruction of all documents will then be made.

The site PI will be responsible for archiving all trial-related documents (including paper worksheets and other essential documents) held at participating Australian sites for 15 years after the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the site complied with the principles of GCP and other applicable regulatory requirements. Guidance on archiving will be provided to sites in a trial-specific SOP.

All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

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Appendix 1 – Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Appendix 2 – Opt-out approach and the National Statement

T4P meets the conditions for an opt- out approach as detailed in the National statement 2.3.6 as follows:

a) involvement in the research carries no more than low risk to participants

This trial, where all trial arms are encompassed by the range of usual care in Australia and New Zealand, confers no greater clinical risk than receiving routine treatment. The follow up phone calls are unlikely to cause any distress to patients or their families and are hence low risk to participants.

b) the public interest in the proposed activity substantially outweighs the public interest in the protection of privacy

This trial will address an important gap in the evidence base and has the potential to provide future guidance for bedside clinicians and optimise important patient-centred outcomes. As such it has significant public interest while privacy is protected by an opt-out approach and study design methods. Refer to protocol section 11.2.2.

c) the research activity is likely to be compromised if the participation rate is not near complete, and the requirement for explicit consent would compromise the necessary level of participation

Participants (when deemed competent) and/or their PR will be approached as soon as reasonably possible after enrolment. An opt-out approach will maintain the right to voluntarily determine participation while easing participant/PR burden in indicating that decision which explicit consent imposes. Refer to protocol section 11.3.1.

d) reasonable attempts are made to provide all prospective participants with appropriate plain language information explaining the nature of the information to be collected, the purpose of collecting it, and the procedure to decline participation or withdraw from the research

All participants and/or their PR will be provided with written and verbal information to facilitate understanding of all aspects of the trial and the procedure for declining participation. Refer to protocol section 11.3.1.

e) a reasonable time period is allowed between the provision of information to prospective participants and the use of their data so that an opportunity for them to decline to participate is provided before the research begins

Participants and/or their PR will be approached at the earliest reasonable opportunity to consider their ongoing participation in the trial. They will have the ability to decline participation at this point or at any future time through the mechanism described in the information brochure. As this encompasses the use of data and follow up telephone calls at day 90 and 12 months they can decline/withdraw from further participation at any time before these time points.

f) a mechanism is provided for prospective participants to obtain further information and decline to participate

The information brochure, as approved by the relevant ethics committee, will contain contact numbers/details on who can provide further information and how to decline participation. Refer to protocol section 11.3.1.

g) the data collected will be managed and maintained in accordance with relevant security standards

The trial will adhere to all relevant data collection security standards. Refer to protocol section 12.

h) there is a governance process in place that delineates specific responsibility for the project and for the appropriate management of the data

The specific responsibilities for the trial itself and the appropriate data management are detailed in protocol sections 3 and 12.

i) the opt-out approach is not prohibited by state/territory, federal, or international law.

The opt-out approach is one of the two possible approaches to consent this study may use. Where opt-out approach is not possible due to local state/territory laws, then consent will be sought as consent to continue as detailed in protocol section 11.3.2.