Study 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)

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All trial investigators have confirmed that they have no financial or other conflicts of interest to declare in relation to this trial.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1 TABLE OF CONTENTS

1 TABLE OF CONTENTS 4
2 KEY CONTACTS 7
3 LAY SUMMARY 8
4 SYNOPSIS 9
5 ABBREVIATIONS 13
6 TRIAL FLOW CHART 15
7 BACKGROUND AND RATIONALE 16
7.1 Review of existing evidence 16
7.1.1 Platelet transfusion and bleeding in critically ill patients 17
7.1.2 Risks of platelet transfusion 17
7.2 Why is this research important to patients and the NHS 18
7.2.1 Health benefits 18
8 AIM, OBJECTIVES AND OUTCOME MEASURES 19
8.1 Aim 19
8.2 Objectives 19
8.3 Outcomes 19
8.3.1 Outcome measures 19
8.3.2 Internal pilot 20
9 STUDY DESIGN 20
9.1 Design 20
9.2 Setting 21
9.2.1 Sites 21
10 PARTICIPANT IDENTIFICATION 22
10.1 Study Participants 22
10.2 Inclusion criteria 22
10.3 Exclusion criteria 23
10.4 Co-enrolment 23
11 PROTOCOL PROCEDURES 24
11.1 Screening 24
11.2 Recruitment and consent 24
11.2.1 Randomisation 24
11.2.2 Consent procedures 24
11.3 Interventions 28

11.3.1 Intervention 28
11.3.2 Co-interventions 29
11.3.3 Monitoring adherence to the intervention 30
11.4 Withdrawal of Participants 30
11.5 Definition of End of Study 30
12 SAFETY REPORTING 30
12.1 Definitions 30
12.2 Assessment 31
12.2.1 Severity 31
12.2.2 Relatedness 32
12.2.3 Expectedness 32
12.3 Recording and reporting procedures 32
12.4 Follow-up after adverse event 33
12.5 Notifying the Research Ethics Committee 33
12.6 Statutory reporting 33
13 Statistics and data analysis 35
13.1 Sample size 35
13.2 Statistical analysis 35
13.2.1 Internal pilot analysis 35
13.2.2 Clinical effectiveness analysis 35
13.2.3 Subgroup analyses 37
13.2.4 Interim analyses 37
13.2.5 Stopping rules 37
13.2.6 Health economic evaluation 37
14 DATA MANAGEMENT 39
14.1 Source Data 39
14.2 Access to Data 39
14.3 Data collection 39
14.4 Questionnaire follow-up 40
14.5 Data management 40
15 QUALITY ASSURANCE PROCEDURES 41
15.1 Risk Assessment 41
15.2 Study monitoring 41
15.2.1 Central monitoring 41

15.2.2 Site monitoring 41
15.3 Study Committees 41
15.3.1 Trial Management Group (TMG) 41
15.3.2 Trial Steering Committee (TSC) 42
15.3.3 Data Monitoring and Ethics Committee (DMEC) 42
15.3.4 Patient and Public Involvement (PPI) 42
16 PROTOCOL DEVIATIONS 42
17 SERIOUS BREACHES 42
18 ETHICAL AND REGULATORY CONSIDERATIONS 43
18.1 Declaration of Helsinki 43
18.2 Guidelines for Good Clinical Practice 43
18.3 Approvals 43
18.4 Reporting 44
18.5 Transparency in Research 44
18.6 Participant Confidentiality 44
18.7 Expenses and Benefits 44
19 FINANCE AND INSURANCE 44
19.1 Funding 44
19.2 Sponsorship and indemnity 44
19.3 Contractual arrangements 45
20 PUBLICATION POLICY 45
20.1 Dissemination 45
20.2 Access to the final trial dataset 46
21 DEVELOPMENT OF A NEW PRODUCT / PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY 46
22 ARCHIVING 46
23 REFERENCES 47
24 Appendix 1 – Amendment history 51
25 Appendix 2 – Expected adverse events 52

2 KEY CONTACTS

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3 LAY SUMMARY

In the United Kingdom (UK), around 250,000 platelet transfusions are given out every year. Platelet transfusions are given when the number of platelets in the blood (the platelet count) falls below a certain level (the transfusion threshold). Platelet transfusions are commonly given in critical care units as patients in critical care often have fewer platelets in their blood than healthy people. In critical care units, platelet transfusions are mainly given to try and prevent bleeding, for example during a procedure.

However, platelet transfusions also have risks, such as an allergic reaction, and may not work as well in critical care unit 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. As a result, a wide range of transfusion thresholds are currently used in critical care units to decide when platelet transfusions should be given.

Therefore, we intend to carry out a large clinical trial to find out the best transfusion threshold below which platelet transfusions should be given to patients who need an invasive procedure in critical care. The study will include 2,550 patients from around 66 UK NHS critical care units. Patients will be randomly allocated (by chance) to one of five platelet transfusion thresholds. If their platelet count drops below their allocated threshold, they will be given a platelet transfusion before their procedure. We will follow up all patients, after 90 days and one year, by 'linking' study data with routinely collected national records. We will work out the best transfusion threshold by comparing the number of patients alive in each group at 90 days.

Patient recruitment will start in mid-2022 and end in 2026. The results will have a large and immediate impact on critical care clinical practice, as well as wider benefits throughout the NHS.

4 SYNOPSIS

Short title	**T**hreshold for **P**latelets (T4P)
Scientific title	The Threshold for Platelets (T4P) 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.
Primary registry and trial identifying number	ISRCTN79371664
Date of registration in primary registry	30 September 2022
Funding	National Institute for Health Research Health Technology Assessment Programme
Sponsor	University of Oxford
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Contact for scientific queries	Professor Peter Watkinson Chief Investigator Tel: 01865 220 621 Email: peter.watkinson@ndcn.ox.ac.uk
Countries of recruitment	United Kingdom
Health condition studied	Thrombocytopaenia in critically ill patients requiring a low risk invasive procedure
Intervention(s)	A single adult equivalent dose (AED) of platelet transfusion, defined according to national specifications, according to one of five platelet thresholds
Trial design	An open label, randomised, Bayesian adaptive, comparative effectiveness trial, including an internal pilot phase, across five equally-spaced platelet count thresholds (<10 - <50x10^9/L) in critically ill adult patients. Interventional

	Allocation: Randomised Blinding: Open label Primary purpose: Prevention
Inclusion and exclusion criteria	Sexes eligible for study: Both Accepts healthy volunteers: No Patients must meet all the inclusion criteria, and none of the exclusion criteria at the time of randomisation: Inclusion criteria: 1. Adult (aged ≥18 years) 2. Accepted for admission or admitted to a participating critical care unit 3. Platelet count <50x10^9/L 4. Planned to undergo a specified* *low bleeding risk invasive procedure* OR platelet transfusion being considered for an 'other' procedure *Specified *low bleeding risk invasive procedures* include the following: • Central venous vascular catheter 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, the following: • Arterial catheter insertion • Arterial or central venous catheter removal • Pleural drain • Interventional radiology (as defined by Society of Interventional Radiology guidelines) • 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 thrombocytopaenia; immune thrombocytopaenia; 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 no. 1 and 2 are dynamic, and if resolved, the patient may be reconsidered for the trial. Patients receiving anticoagulation therapy or anti-platelet therapy will be included, with unit policies (other than platelet administration) followed prior to the procedure. Patients with platelet counts ≥50x10^9/L will be screened daily until recruitment, refusal or critical care unit discharge. Patients undergoing procedures not eligible for randomisation will remain available for inclusion where subsequent eligible procedures occur.
Date of first enrolment	Anticipated July 2022
Target sample size	2,550
Follow up duration	12 months
Planned trial period	60 months
Primary outcomes	90-day all-cause mortality

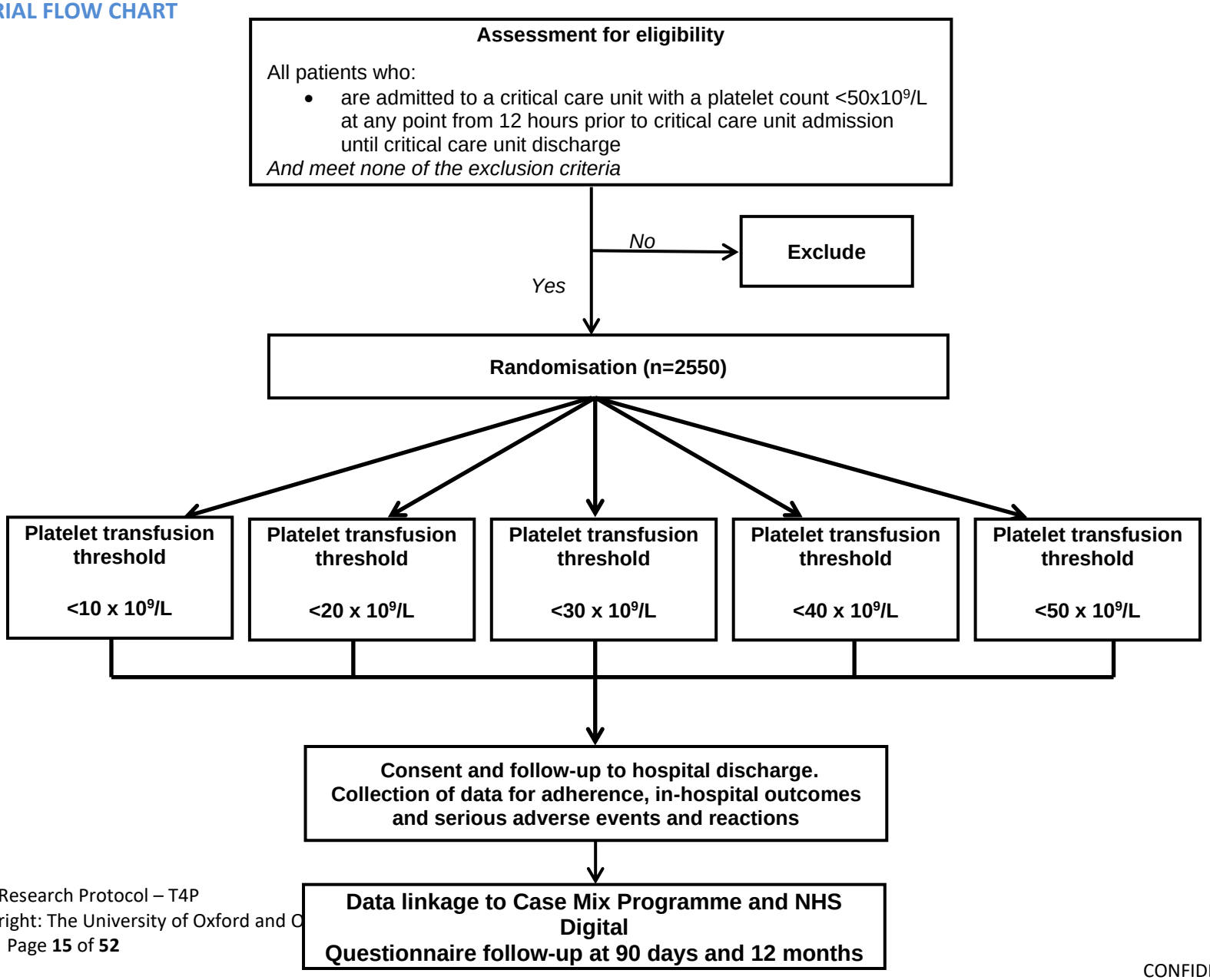
Secondary outcomes	• Mortality at discharge from critical care unit, hospital and at one year • Survival to longest available follow-up • Rates of *major* and *fatal* bleeds classified according to the HEME bleeding score • Venous and arterial thromboses in hospital and to one year • Duration of renal, 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)
Economic outcomes	Primary cost-effectiveness outcome: • Net monetary benefit (NMB) at 90 days Secondary cost-effectiveness outcomes: • NMB at one year • Resource use and costs at 90 days and one year
Subgroup analyses	Where numbers allow, we will repeat the analysis in the following patient subgroups: • Bone marrow failure • Hepatic failure • Sepsis

5 ABBREVIATIONS

AE	Adverse event
AED	Adult Equivalent Dose
APML	Acute promyelocytic leukaemia
CCMDS	Critical Care Minimum Dataset
CEA	Cost-effectiveness analysis
CI	Chief Investigator
CMP	Case Mix Programme
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring & Ethics Committee
EQ-5D-5L	European Quality of Life Scale
GCP	Good Clinical Practice
HAT	Hospital-acquired (or -associated) Thrombosis
HEME	HEmorhage Measurement
HES	Hospital Episode Statistics
HRG	Healthcare Resource Group
HrQoL	Health-related quality of life
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
LOS	Length of Stay
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
NMB	Net monetary benefit
PI	Principal Investigator
PICRAM	Post Intensive Care Risk Adjusted Monitoring study and database
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance. University of Oxford
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VTE	Venous thromboembolism

6 TRIAL FLOW CHART



7 BACKGROUND AND RATIONALE

United Kingdom (UK) blood services issued 252,000 platelet transfusions in 2018. After cancer services, critical care units use most platelets (1, 2), where platelet transfusions are mainly given to prevent spontaneous or procedure-induced bleeding in patients with low platelet counts (thrombocytopaenia) (1). However recent trials outside adult critical care show platelet transfusions may cause harm (3, 4). Our systematic review and others highlight a lack of evidence on safety and benefits of prophylactic platelet transfusions (5, 6). Recent practice guidelines are unable to recommend a platelet count below which giving platelets confers benefit rather than harm, so call for new research (1, 7, 8).

Typical trial designs, comparing two maximally separated platelet count thresholds below which platelets are transfused (for example 20 versus $50x10^9$/L (9, 10) are unlikely to identify optimal thresholds. To establish the platelet threshold below which platelet transfusion confers a cost-effective patient benefit, we will undertake a novel, randomised adaptive comparative effectiveness trial allowing simultaneous study of multiple platelet thresholds to define the optimum threshold by modelling a threshold-response curve. Refining the methodology in this study will allow use in other threshold-defined (for example renal replacement (11, 12)) or time-defined (for example tracheostomy (13)) interventions.

7.1 Review of existing evidence

Thrombocytopaenia is common in critically ill patients, with up to 12% having platelet counts $<50x10^9$/L at any point in their stay (14). Analyses of two UK databases - the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP) database (containing data on all admissions to adult general critical care units in England, Wales and NI) and PICRAM (HICF 16/111/136) database, including 11,000 patients from three Thames Valley critical care units – showed that 4500 patients are admitted to adult general critical care units participating in the CMP with platelet counts $<50x10^9$/L, annually whilst PICRAM data show another 3100 patients develop platelet counts $<50x10^9$/L during their critical care unit stay. Patients may have low platelet counts because of critical illness, treatments or underlying bone marrow failure.

Platelet transfusion in critically ill patients is common. Our 29 UK critical care unit based study showed 9% of all critical care unit patients receive a platelet transfusion (14). Most of these transfusions are given prophylactically (to reduce the chance of future bleeding rather than for acute bleeding) (14, 15).

The range of platelet counts over which platelet transfusions are given to critically ill patients is wide (14, 16), though the majority occur in patients with a platelet count $<50x10^9$/L (17). In our recent survey of current clinical practice within UK critical care units (18), platelet transfusion thresholds prior to a low bleeding risk invasive procedure were common anywhere in the range <10 - $50x10^9$/L. Only 5% of respondents reported using higher thresholds for minor procedure prophylaxis.

7.1.1 Platelet transfusion and bleeding in critically ill patients

Major spontaneous bleeding occurs in ~16% of patients on a critical care unit with platelet counts <100x10^9/L (19). However, retrospective studies conflict about whether lower platelet counts are associated with increased episodes of bleeding (20-22). Despite common use, it is unclear whether platelet transfusions reduce bleeding in critically ill patients (23). The small numbers involved in these studies hamper meaningful interpretation.

In comparison to the other major group of patients receiving donor platelets (haematological malignancy) where average platelet count increments of 25x10^9/L per platelet transfusion occur outside a critical care unit (24, 25), increments in critically ill patients are often lower at around a median of 15 (2-36 10^9/L) (14). Analysis of the PICRAM database shows patients with haematological malignancy on a critical care unit have similarly low increments suggesting that guidance for these patients outside a critical care unit cannot be translated into their critical illness (17). These lower increments may limit the ability of platelet transfusions to prevent bleeding in critically ill patients. In the only platelet prophylaxis RCT in critically ill patients (one centre, 57 patients undergoing percutaneous tracheostomy), intratracheal bleeds were evenly spread between patients who did or did not receive platelets (26). In a small (57 critically ill patients with liver cirrhosis) three arm study of transfusion protocols (comparing thresholds for platelets, fresh frozen plasma and cryoprecipitate) there was no major bleeding in 19 patients transfused below a platelet threshold of 25x10^9/L or in the 19 transfused below a platelet threshold of 50x10^9/L (4 versus 2 minor bleeding) (27). In non-critically ill patients with haematological malignancies, platelet prophylaxis has a small effect on the incidence of bleeding (28, 29). Many patients experience bleeding despite receiving a platelet transfusion. However major bleeding (World Health Organisation grades 3 or 4) is less common (~2%) than in thrombocytopaenic patients treated on a critical care unit (19, 28) whose higher baseline bleeding risk (~16%) may make transfusion at higher platelet count thresholds beneficial.

7.1.2 Risks of platelet transfusion

There are significant risks associated with receiving platelets. Critically ill neonates randomised to liberal prophylactic platelet transfusion had higher mortality and more frequent major bleeds than those with a restrictive strategy (50 versus 25x10^9/L) (4). An RCT in adults with intracerebral haemorrhage found higher mortality and impaired recovery with liberal platelet transfusion (3). In systemically inflamed critically ill patients, platelet transfusion is associated with the acute respiratory distress syndrome (30-32), nosocomial infection (33), venous and arterial thromboses (34, 35) increased critical care unit length of stay (LOS) and death (36). These complications are biologically plausible as platelets mediate multiple physiological processes beyond clotting, including interactions with immunological pathways. The Serious Hazards of Transfusion (SHOT) national UK haemovigilance system provides data on all immediate transfusion reactions. Analysis of the last 8 years data for this application shows serious reactions to be twice as common with platelet transfusions compared to other blood components including red cells (SHOT Director Dr Narayan, personal communication).

These findings, taken together, demonstrate the need for a definitive, large, multi-centre, RCT to evaluate the optimum platelet threshold below which platelets should be transfused prior to an invasive procedure in critically ill patients.

7.2 Why is this research important to patients and the NHS

7.2.1 Health benefits

Uncertainty about when to give platelets creates inconsistent practice, with critically ill patients receiving platelets over a wide range of transfusion thresholds (14, 16). Platelet transfusions are biological agents. Two recent RCTs showed harm to patients outside adult critical care, making research urgent (3, 4).

7.2.1.1 Economic benefits

Retrospective work suggests optimal platelet use may decrease critical care unit and hospital LOS, reducing costs (36). If our study indicates a restrictive platelet transfusion practice, reducing transfusions by 30%, as has been achieved outside adult critical care (4, 28), this would result in 8000 fewer platelet transfusions given annually, saving £2.1M (37, 38).

7.2.1.2 Health and Care service benefits

Critical care units give 9% of all platelet transfusions in the UK (1). The falling donor base (1) makes research to optimise platelet use timely.

The NHS Health Service Circular (HSC 2007/001) (39) calls for further action to reduce the unnecessary use of blood components, and in particular, platelet transfusions. The National Blood Transfusion Committee's *Patient Blood Management* recommendations (supported by NHS England) support this call and have asked for the commissioning of high-quality clinical trials on safe and effective transfusion practice (40). The James Lind Alliance's (JLA's) blood transfusion and donation partnership placed discouraging inappropriate blood product use the second highest research priority (41).

Internationally, the need for research was re-iterated by the 2018 Frankfurt international consensus conference (42) and also forms a key basis of other national patient blood management programmes including the International Society of Blood Transfusion (ISBT, www.isbtweb.org and the AABB (www.AABB.org) (43). Identifying the minimum safe platelet count prior to performing an invasive procedure has been highlighted as a high research priority by the AABB Clinical Practice Guidelines on Platelet Transfusion (44).

The 2020 European Society of Intensive Care Medicine practice guidelines (whilst acknowledging the one RCT of central line insertion in patients outside and within a critical care unit (10) recommend that research be undertaken in patients requiring critical care to determine platelet transfusion thresholds between 10 and $50x10^9$/L.

8 AIM, OBJECTIVES AND OUTCOME MEASURES

8.1 Aim

The aim of T4P is 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.

Research question: In critically ill patients, what is the optimum platelet threshold below which platelets should be transfused prior to an invasive procedure?

Study 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.

8.2 Objectives

- To model the threshold-response curve for the effect of platelet transfusion prior to/during an invasive procedure in critically ill patients.

- 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.

8.3 Outcomes

8.3.1 Outcome measures

Primary outcomes – clinical effectiveness:

- All-cause mortality at 90 days.

Primary outcomes – cost-effectiveness:

- Incremental costs, QALYs and net monetary benefit at 90 days.

Secondary outcomes:

- Mortality at discharge from critical care unit, 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 (45)
- 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
- NMB at one year.

8.3.2 Internal pilot

The pilot phase will cover the first 12 months of recruitment and will use a traffic light system (46) for three measures of recruitment of sites and patients and adherence to protocol. The thresholds to assess progression from the internal pilot phase to full trial are:

	Red	Amber	Green
Recruitment rate (per site per month)	<50% of anticipated	50-99% of anticipated	100% of anticipated
Proportion adhering to assigned platelet threshold at first included procedure	<75%	75-99%	100%
Number of sites opened	<30	30-65	66

Table 2: Progression criteria

If all the green criteria are met, the trial will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, we will take remedial action and the study will be amended to address the issues raised. If any of the red criteria are met, we will discuss urgently with the Trial Steering Committee (TSC) and the funder and consider remedial actions, including discontinuation. A pilot phase report will be reviewed by the TSC and any required remedial plans developed before a pilot phase report is submitted to the NIHR HTA.

9 STUDY DESIGN

This Protocol has been written in accordance with the SPIRIT-PRO guidelines (47, 48).

9.1 Design

T4P is an open label, randomised, Bayesian adaptive comparative effectiveness trial including an internal pilot phase across five equally-spaced thresholds of thrombocytopaenia (<10 - <50x10^9/L).

9.2 Setting

9.2.1 Sites

Sixty-six NHS Hospitals containing a critical care unit within the Case Mix Programme. Study interventions will occur in the admitting critical care unit, in the Emergency Department prior to critical care unit admission, or where in the hospital the procedure takes place if it precedes a critical care unit admission.

9.2.1.1 Site requirements

- Active participation in the CMP
- Compliance with all responsibilities as stated in the T4P Clinical Trial Site Agreement
- Compliance with all requirements of the trial protocol
- Compliance with the UK Policy Framework for Health and Social Care Research and the principles of Good Clinical Practice (GCP).

9.2.1.2 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 (https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm)
- Identify a T4P research nurse 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 and ensure adherence with the trial protocol
- Agree to aim to randomise all eligible patients and to maintain a Screening Log
- Agree to data collection requirements.

9.2.1.3 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. local confirmation of capacity and capability)
- A fully signed T4P Clinical Trial Site Agreement
- A completed Delegation Log.

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the PIs, 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 Good Clinical Practice (GCP) requirements

- Appropriate means to identify and randomise eligible patients into the trial
- Timely data collection, entry and validation; and
- 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 ICNARC CTU 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).

10 PARTICIPANT IDENTIFICATION

10.1 Study Participants

Critically ill adults admitted to, or requiring admission to, a critical care unit who have low platelet counts 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**:

10.2 Inclusion criteria

1. Adult (aged ≥18 years)
2. Accepted for admission or admitted to a participating critical care unit
3. Platelet count <50x10^9/L
4. Planned to undergo a specified* *low bleeding risk invasive procedure* OR platelet transfusion being considered for an 'other' procedure

*Specified *low bleeding risk invasive procedures* include the following:

- Central venous vascular catheter 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, the following:

- Arterial catheter insertion

- Arterial or central venous catheter removal
- Pleural drain
- Interventional radiology (as defined by Society of Interventional Radiology guidelines)
- 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

10.3 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 thrombocytopaenia; immune thrombocytopaenia; 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 no. 1 and 2 are dynamic, and 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.

10.4 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 onto other interventional studies where there is no possible conflict with the T4P objectives. We will follow previous experience and existing guidelines from the Intensive Care Society regarding co-enrolment to other clinical trials to maximise patient involvement in research. Co-enrolment agreements will be put in place on a trial-by-trial basis.

11 PROTOCOL PROCEDURES

11.1 Screening

At the point of the decision to admit to a critical care unit, potentially eligible patients will be screened against the inclusion/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 a critical care unit, patients with platelet counts $\geq 50x10^9$/L will be screened daily until recruitment, refusal or critical care unit discharge. Once a patient first meets all inclusion criteria and none of the exclusion criteria, they should be randomised within 72 hours.

11.2 Recruitment and consent

11.2.1 Randomisation

Randomisation will occur as soon as possible (<72 hours) after confirming eligibility. 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 CRF will be completed by the local team (*see section 14.3*).

11.2.2 Consent procedures

Patients eligible for T4P become so during a period of critical illness. Time-critical invasive procedures often occur in the first hours of a critical care unit admission. Analysis of the PICRAM data set and the NHSBT led DRIVE (Desmopressin for procedures or Radiological InterVEntions) study (49) dataset 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 a Personal Consultee (i.e. relative or close friend) to provide an opinion about trial participation during a time of great distress. In addition, delaying the clinical procedure while an urgent opinion from a Personal Consultee is sought would not represent usual clinical practice and might delay essential treatment. For these reasons, attempts to obtain either prior informed consent from the patient, or the prior opinion of a Personal Consultee, are inappropriate. In the situation where a Personal Consultee is available, in person, at the time the patient becomes eligible for inclusion into the trial, and if it is deemed appropriate, the Personal Consultee will be presented with a short information leaflet that provides an overview of the trial and consent procedures. Due to the time-sensitive nature of the invasive procedures, if the Personal Consultee does not provide any

objection to the patients' participation, the patient will be enrolled, and consent obtained from the personal consultee and/or patient following the procedures described below.

T4P will adopt a research without prior consent (RWPC) model (also referred to as 'deferred consent'), whereby eligible patients will be randomised to receive the assigned treatment as soon as possible. This is an accepted consent model in adult emergency and critical care research where participants lack mental capacity (50) and minimises the distress and additional burden on families. In addition, the urgent nature of time-critical invasive procedures and treatments delivered in a critical care unit means that any delay to commencing treatment could be detrimental to the patient (and to the scientific validity of the trial). This consent model is covered by an Emergency Waiver of Consent under the Mental Capacity Act (approved by [South Central – Oxford C] Research Ethics Committee (reference: [22/SC/0186])).

In the very rare situation where a patient has been deemed by the treating clinical team to have full mental capacity and is able to give informed consent at the point of meeting the eligibility criteria, they will be approached directly prior to randomisation for verbal or other non-written (e.g. through blinking or hand movement) consent to take part in T4P. If they provide verbal or other non-written consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 11.2.2.1. If such a participant who gave prospective verbal/non-written consent subsequently lost mental capacity, the opinion of a Personal or Nominated Consultee must be sought to advise on their continuation in the trial (*see sections 11.2.2.2 and 11.2.2.3*).

11.2.2.1 Patient informed deferred consent

Following randomisation, patients will be approached by a delegated member of the site research team once deemed to have full capacity to provide informed deferred consent. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity. A Participant Information Sheet (PIS) will be given to the patient. The PIS will provide information about the background/rationale for the trial, what participation means for the patient (e.g. data collection, follow-up questionnaires), confidentiality and data protection and the future availability of the trial results. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in T4P.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence. The Consent Form will also cover consent for access to medical records for ongoing data collection and follow-up.

After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator

Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness (not involved in the trial) can sign on their behalf.

In the situation where a patient is approached in hospital but wishes to have more time to consider participation, they can request to be approached via the method detailed in section 11.2.2.4.

11.2.2.2 Personal Consultee Opinion

It will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into T4P, a delegated member of the site research team will approach the Personal Consultee (in person or via telephone) as soon as appropriate and practically possible to discuss the trial and seek their opinion as to the patients' likely wishes and feelings regarding participating in the trial. Ideally, this approach would take place within 24-48 hours of randomisation, but once the patient's medical situation is no longer an emergency.

Where approached in person, the Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented with information on why the Personal Consultee has been approached at this stage. Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the T4P study.

A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in the trial.

After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the person seeking opinion will invite the Personal Consultee to sign the Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in the trial, then the trial treatment will be stopped (if ongoing) and the Personal Consultee asked whether, in their opinion, the patient would be willing to continue with ongoing data collection.

Where a Personal Consultee is unable to visit the patient in hospital (e.g. due to infection control measures), this consultation may take place over the telephone. The consultation should be conducted by an experienced member of the site research team with knowledge of intensive care. The telephone consultation should be witnessed by another member of staff. The Personal Consultee Information Sheet may be sent to the Personal Consultee by email or by post. The outcome of the consultation will be

documented and signed by person seeking opinion on the Personal Consultee Telephone Opinion Form, countersigned by the witness.

Upon patient recovery, the patient will be approached directly for informed deferred consent (*see section 11.2.2.1*). The patient's decision will be final, and will supersede the Personal Consultee, where there is disagreement.

11.2.2.3 Nominated Consultee Opinion

A Nominated Consultee will be approached in the rare situations where no Personal Consultee is available (or one is available, but does not wish to be consulted). Upon patient recovery, the patient will be approached directly for informed deferred consent (*see section 11.2.2.1*). The patient's decision will be final, and will supersede the Nominated Consultee, where there is disagreement.

The Nominated Consultee may include an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust or an independent appropriately qualified clinician (not involved in the trial). Opinion of the Nominated Consultee will be sought in the same manner as for the Personal Consultee.

11.2.2.4 Discharge prior to consent/opinion being confirmed

In the situation where the patient is discharged from hospital with mental capacity prior to confirming their consent decision, an experienced member of the site research team with knowledge of intensive care will attempt a phone call to the patient within 14 working days of ultimate hospital discharge to: inform them of their involvement in T4P; provide information about the trial; and seek their consent. The telephone consultation should be witnessed by another member of staff. The Patient Information Sheet may be sent to the patient by email or by post. The outcome of the telephone call will be documented and signed by person seeking consent on the Telephone Consent Form, countersigned by the witness.

If there is no response to at least three telephone call attempts, or, where no telephone number for the patient is documented, then the patient will be approached by post. The patient will be sent a covering letter, personalised by the most appropriate clinical/research team member, and a copy of the PIS and Postal Consent Form. The letter will direct the patient to the PIS for detailed information on the trial and provide contact details for if the patient wishes to discuss the trial further. In addition, the letter will confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant's data will be included in the trial unless they notify the site research team otherwise.

Both methods described above will provide patients with the opportunity to opt out of ongoing data collection or follow-up questionnaires. A decision to opt out during the telephone call will be documented by the person seeking consent on the Telephone Consent Form. For the postal approach, the patient can opt out using the telephone contact details provided on the PIS, at any point during the trial.

If the participant is transferred to another hospital participating in T4P before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

If the participant is transferred to another hospital who are not participating in T4P before the consent procedures are complete, then the local research team will contact the receiving hospital for outcome data. Meanwhile, Personal Consultee or local Nominated Consultee opinion should be sought as appropriate. The patient consent procedure will be followed as appropriate following ultimate hospital discharge.

In the situation where a patient is discharged from hospital without regaining mental capacity, the Personal Consultee decision will be final.

11.2.2.5 Refusal or withdrawals of consent/opinion

If a patient declines informed deferred consent, or a consultee advises that they believe the patient would not choose to participate in the trial, and, if a patient or their Consultee (Personal or Nominated) withdraws consent/opinion at any time during the trial - this decision will be respected and will be abided by. All data up to the point of this decision will be retained in the trial unless the patient or consultee requests otherwise. Where possible, patients and consultees will be asked if they are happy for data to continue to be collected from the medical records for the trial, emphasising that this will not require any further contact with the patient/consultee about the trial.

11.3 Interventions

11.3.1 Intervention

Patients will be randomised to one of five equally-spaced platelet thresholds (<10 - <50x10^9/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.

Treatment according to the randomly allocated threshold will continue for all subsequent low bleeding risk invasive procedures (*see section 10.2*) until critical care unit 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 a critical care unit during the index hospital stay within the 90 days, treatment according to the randomly allocated threshold will be recommenced. Procedures occurring after critical care unit discharge are at discretion of the clinical team and do not need to follow the allocated treatment threshold.

The study intervention is specified in Template for Intervention Description and Replication (TIDieR, (51) format below:

TIDieR item number	Item descriptor	Item
1	Brief name	Platelet transfusion for procedures
2	Why	Platelet transfusion according to designated platelet threshold around invasive procedures is aimed at decreasing bleeding, but may increase mortality by increasing infection, inflammation or thrombosis
3	What materials	A platelet component, as specified in national policies (Guidelines for the Blood Transfusion Services in the UK: https://www.transfusionguidelines.org/red-book)
4	What procedures	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 meeting the definition for inclusion or those deemed as low bleeding risk by the treating clinician until critical care unit discharge.
5	Who provides	The responsible clinicians (medical and nursing)
6	How	Bedside care throughout administration
7	Where	Participating hospitals creating a study population representative of the UK population treated on a critical care unit.
8	When and how much	A single adult equivalent dose (AED) delivered immediately prior/during the procedure
9	Tailoring	Platelets for significant bleeding post-procedure can be given at the clinician's discretion
11*	How well	Intervention adherence will be monitored during the trial in the study CRF by trained trial research staff.

Table 1. *Items 10 and 12 are not applicable until study completion

11.3.2 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.

11.3.3 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

11.4 Withdrawal of Participants

Refer to section 11.2.2.5.

11.5 Definition of End of Study

The end of the trial is defined as last patient, last 90-day follow-up. At this point, the 'Declaration of end of trial' form will be submitted to the REC by the ICNARC CTU.

12 SAFETY REPORTING

12.1 Definitions

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting in studies which do not use Investigational Medicinal Products (non-CTIMPs).

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.

Unexpected and Related Serious Adverse Event
A suspected Adverse Event related (possibly, probably or definitely) to the trial treatment that is both unexpected (i.e. not consistent with the expected outcomes of the treatment being offered) and serious.

12.2 Assessment

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

12.2.1 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).

12.2.2 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.

12.2.3 Expectedness

- **Expected**: the event is listed as an expected SAE in Appendix 2 – Expected adverse events
- **Unexpected**: the event is not listed as an expected SAE in Appendix 2 – Expected adverse events

12.3 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 critical care unit discharge. If a patient is readmitted to the critical care unit 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 (52) – occurrences of non-specified, unexpected, SAEs will only be reported if they are considered to have reasonably 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 ICNARC CTU 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 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. 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 sent by email to T4P@icnarc.org.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1: Adverse Event recording and reporting.

On receipt of an SAE report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the T4P Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC). If the event is evaluated by either the Chief Investigator or a clinical member of the T4P TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days of the Chief Investigator becoming aware of the event, using the HRA serious adverse event form (see HRA website).

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

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

12.4 Follow-up after adverse event

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to the ICNARC CTU by updating the T4P SAE Report Form on the electronic data entry system. Any updates to the SAE Report Form will require electronic sign-off by the PI (or medically qualified delegate). AEs and SAEs should be followed up until resolution or death of the trial subject.

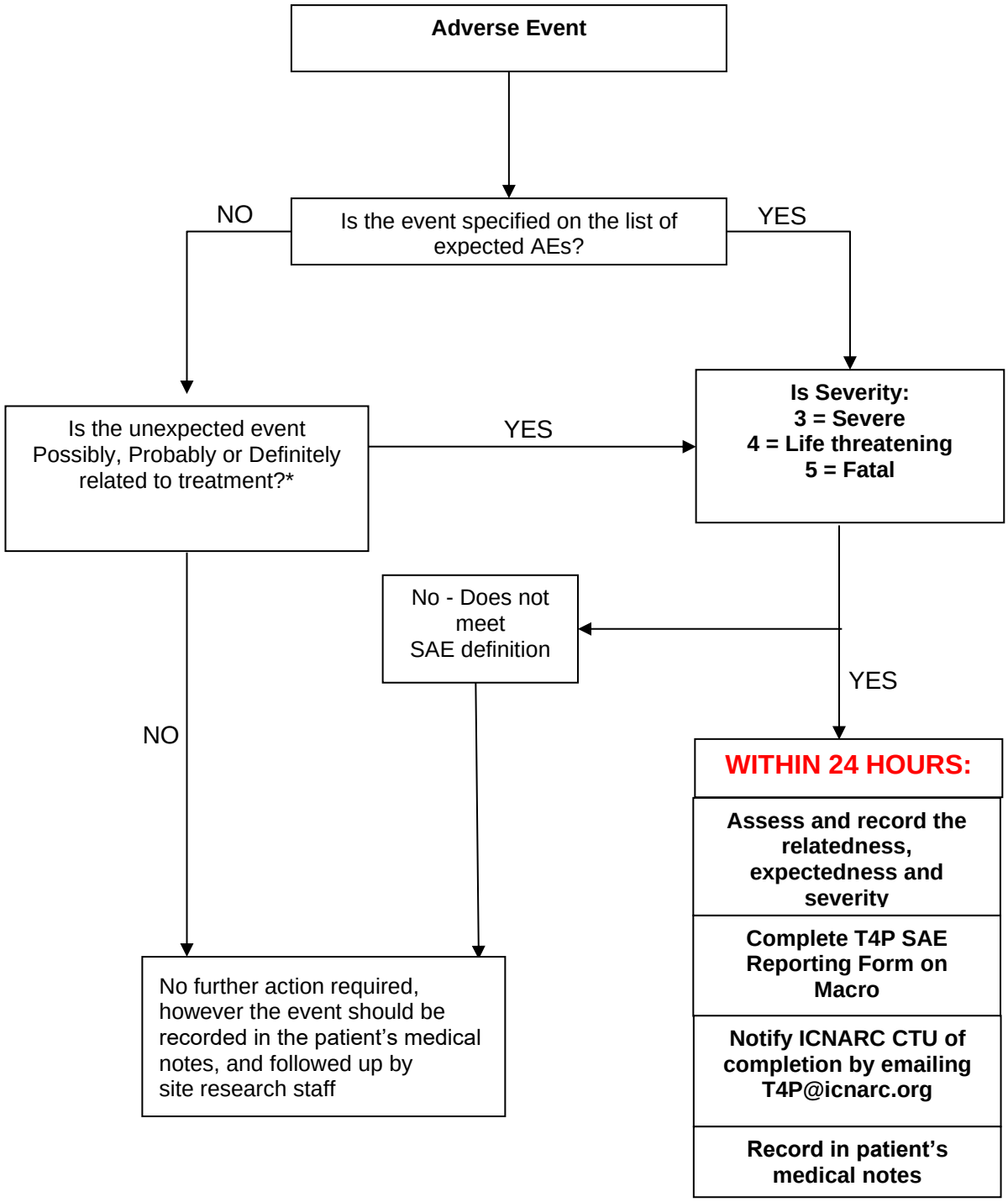
12.5 Notifying the Research Ethics Committee

SAEs that do not require expedited reporting will be reported in the annual progress report submitted by the ICNARC CTU to the REC, commencing one year from the date of approval for the trial.

12.6 Statutory reporting

Transfusion reactions that constitute a SAE should be reported to the medical team responsible for statutory reporting to SHOT/SABRE according to standard procedures, as required by the UK Blood Safety and Quality Regulations 2005.

Figure 1: Adverse Event recording and reporting



*If there is any uncertainty about whether the SAE is associated with trial treatment, then it should be reported.

13 Statistics and data analysis

13.1 Sample size

We estimated the sample size from simulations across 7 hypothesised threshold-response curves for the 90-day mortality primary outcome (see simulations appendix for details, located online 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). We increased the sample size to 2550 patients to allow for 6% refusal/withdrawal of consent post-randomisation (as in the "65" Trial (53)).

From the CMP and PICRAM databases, we estimate approximately 4.4% of all admissions will be eligible (conservative, in comparison to published data). The 66 critical care units average 800 admissions/year. Allowing 6 months ramp up to full site numbers, and anticipated recruitment of one from an estimated three eligible patients per site per month, recruitment will complete in 42 months.

13.2 Statistical analysis

13.2.1 Internal pilot analysis

The pilot phase will cover the first 12 months of recruitment, assessing recruitment, willingness to randomise, protocol adherence and data quality. Data will be analysed at the end of the internal pilot trial stage. The analysis will take place in month 20 of the trial to allow data to be collected and entered to assess all progression criteria. If all the green criteria are met, the trial will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, we will take remedial action and the study will be amended to address the issues raised. If any of the red criteria are met, we will discuss urgently with the Trial Steering Committee (TSC) and the funder and consider remedial actions, including discontinuation.

The final decision on progression from the pilot stage to the full trial will be made by the NIHR HTA programme after recommendation by the TSC.

13.2.2 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 (54). 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 (55). 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. NHS 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 (68). 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 (CMP and HES), across treatment groups. Where matching data are insufficient or where linkage has been unsuccessful to either core dataset, all outcomes derived from linked data for that patient will be treated as missing.

13.2.3 Subgroup analyses

We will undertake pre-determined analyses, where numbers are sufficient, of patient groups with:

- Underlying bone marrow failure (defined as a white cell count <1.0 x 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 critical care unit admission or severe chronic liver disease - biopsy proven cirrhosis, portal hypertension or hepatic encephalopathy (56))
- Sepsis (defined according to Sepsis-3 criteria (57), with primary and secondary sepsis considered separately and together).

13.2.4 Interim analyses

We will carry out 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 the 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.

13.2.5 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 (see Section 4.2.4). However, the trial could be stopped if the DMEC raises concerns about harms. Any decision to terminate the trial would be made by the TSC in conjunction with the trial funders.

13.2.6 Health economic evaluation

A full cost-effectiveness analysis (CEA) will be undertaken. The CEA will take a health and personal health services perspective and will measure resource use associated with delivering the intervention, length of stay in critical care and acute hospital, and use of personal health services. Patient-level resource use data for critical care and hospital stays will be taken from the CRF and linked to routine data from the CMP and HES for efficiency.

We will measure those categories of resource use where differences, according to the platelet threshold, may be anticipated to drive incremental costs, including resource use associated with the study intervention (including platelet and equipment use), in-critical care unit organ support, index admission critical care unit and ward LOS, hospital readmissions, and visits to outpatients and community healthcare services (including, for example for anticoagulation management). Each critical care episode will be assigned a Healthcare Resource Group (HRG) by applying a standard HRG grouper algorithm (58). Readmissions to critical care will be accessed from the CMP database, and other readmissions from linkage to HES.

The use of hospital outpatient visits and community services (e.g. GP visits) following discharge from the index admission, but before 90 days and one-year post randomisation will be collected via a health service questionnaire sent to patients at each of these time-points.

The unit costs of each critical care bed day by HRG, and of each general medical bed day will be taken from the 'Payment by Results' database (59) and for hospital outpatient visits and community service use from a recommended published source (60). Patient-level resource use data will be combined with unit costs to calculate total costs per patient to 90 days, and one year following randomisation. Thromboembolism costs will take into account diagnosis, clinic and anticoagulation costs.

HRQoL at 90 days and one year, will be assessed with the EQ-5D-5L questionnaire (61), successfully used to assess patient-reported health status in previous critical care unit trials (62). The responses to the EQ-5D-5L questionnaire will be used to report each patient's described health, and then valued according to the EQ-5D-3L cross-walk algorithm (63), or with an updated UK valuation set if recommended by NICE. QALYs at 90 days and one-year post-randomisation will be calculated by valuing each patient's survival time by their HRQoL at 90 days and one-year according to the "area under the curve" approach (63).

We will calculate NMB at one year by valuing the QALY for each strategy according to NICE recommended levels of willingness to pay for a QALY gain (£20,000), and subtracting from this the total cost for that strategy. We will estimate the NMB threshold-response curve with the same linear regression approaches as for clinical effectiveness outcomes. The cost-effectiveness of standardising practice to the optimum threshold compared with current usual practice will be evaluated by comparing the estimated NMB at the optimum threshold with the NMB across the distribution of thresholds reported in the clinician practice survey.

The CEA will use bivariate regression models to allow for correlation between costs and QALYs, adjusting for the same baseline covariates as for the clinical analysis (64). 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.

We will subject the CEA results to sensitivity analyses including: alternative time horizons (extrapolations to 5 year and to the lifetime), different approaches to handing missing EQ-5D-5L data, and contrasting regression models allowing for the likely skewed nature of the cost data (Normal-Gamma vs Bivariate Normal regression models).

14 DATA MANAGEMENT

14.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These may include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

14.2 Access to Data

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

14.3 Data collection

To maximise efficiency, trial data collection will be nested within the Case Mix Programme national clinical audit. Data from the Case Mix Programme to be used in T4P will include:

- Baseline demographics, severity of illness and risk factors;
- Secondary outcomes of critical care unit and acute hospital mortality, organ support (calendar days of organ support in critical care for the CCMDS), duration of critical care and acute hospital stay; and
- Critical care costs, based on Health Care Resource Groups, from the index admission and any subsequent critical care readmissions

All patients recruited into the trial will be asked to provide consent for data linkage with other routine data sources. Data from other sources will include:

- Date of death for deaths occurring after discharge from acute hospital, by data linkage with civil registrations mortality data held by NHS Digital, until longest available follow-up (e.g. patients recruited in the first month of the trial will be able to be followed-up for survival until 24 months);
- Thromboembolism occurrence and hospital costs for subsequent hospitalisations by data linkage to Hospital Episode Statistics held by NHS Digital and Patient Episodes Data for Wales held by Digital Health and Care Wales; and
- Thromboembolism occurrence will also be obtained from the NICE-mandated hospital-acquired venous thromboembolism (VTE) audit (also known as hospital-acquired or hospital-associated thrombosis (HAT)).

A small amount of additional data items will be collected specifically for the trial. Data will be entered at site onto an electronic CRF, where they will undergo checks for accuracy, completeness and consistency. Additional data items to be collected at each site will include, but are not limited to:

- Patient and consultee contact details and update preferences (to allow for questionnaire follow-up at 90 days and one year)
- Confirmation of eligibility criteria and patient/consultee consent
- Data to monitor adherence with the protocol and randomised platelet transfusion threshold;
- Data on procedures undertaken, response to bleeding episodes and co-interventions; and
- Adverse event reporting.

14.4 Questionnaire follow-up

Each participant will be followed up with a questionnaire up to a maximum of one year (to reduce study duration, one-year follow-up will be curtailed when the final participant reaches the 90-day follow-up, censoring ~20% of participants for one-year outcomes).

Survival status at 90 days and one year following randomisation will be obtained via participating sites and/or data linkage with nationally held routine data. At each time point, survivors will be sent (via email or post as per their indicated preference at the time of consent) a questionnaire by the ICNARC CTU containing the EuroQol EQ-5D-5L and health services questionnaires. These questionnaires are designed to take no longer than 15 minutes to complete and if completing a postal questionnaire, patients will be provided with a pen and stamp-addressed envelope for ease of return.
Non-responders will be telephoned three weeks after the questionnaire was posted and asked to check whether they have received the questionnaire. If preferable for the patient, they will be offered the option of either being sent another copy of the questionnaire, completing the questionnaire over the telephone with a trained member of the T4P Trial team, or to receive the questionnaire in a preferred alternative format (e.g. e-mail).

If a patient is an in-patient at a participating site at either of the follow-up time-points, the site research team will be asked to 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.

14.5 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper worksheets will be available to the sites. The site PIs will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PIs to qualified members of the research team.

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 Data Protection Act (Registration number: Z6289325).

15 QUALITY ASSURANCE PROCEDURES

15.1 Risk Assessment

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

15.2 Study monitoring

15.2.1 Central monitoring

The ICNARC CTU will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of consent forms and essential documents. Data will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

15.2.2 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). Around 25% of 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.

15.3 Study Committees

15.3.1 Trial Management Group (TMG)

The TMG comprises the T4P Investigators (*see T4P Investigators*, *page 1-2*) and will be led by Chief Investigator, Professor Peter Watkinson. Meeting of the TMG will be held quarterly, or more frequently during key stages of the trial, to ensure effective communication.

The day-to-day trial team will be led by the Trial Manager (Ms Hayley Noble) and comprise the Chief Investigator (Professor Peter Watkinson, Clinical Trials Unit co-investigators (Professor David Harrison,

Mr Paul Mouncey, Dr Doug Gould, Dr James Doidge), alongside the Trial Statistician, Research Assistants and Data Manager. The day-to-day trial team will meet regularly to discuss and monitor progress.

15.3.2 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e. consist of 75% independent members – including the Chair). The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder 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 will comprise of the Chief Investigator, a senior representative from the ICNARC CTU and independent members (including independent PPI representatives). Representatives from the Sponsor and Funder will be invited to observe TSC meetings which will be scheduled to take place at the following time points: (1) prior to the start of the trial; (2) following the internal pilot stage; (3-5) during the trial recruitment period; and (6) at the end of primary analysis.

15.3.3 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set up to monitor recruitment and retention, protocol adherence (including adherence to treatment protocols) and patient safety, and will review the interim analysis. Meetings will take place immediately prior to TSC meetings.

15.3.4 Patient and Public Involvement (PPI)

One co-investigator is a PPI representative who has actively contributed to the trial design and procedures, including the use of deferred consent. In addition, independent PPI representative(s) will be sought for membership of the TSC.

16 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.

17 SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the trial subjects; or

(b) The scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

18.2 Guidelines for Good Clinical Practice

T4P will be managed by the ICNARC CTU according to the Medical Research Council's Good Research Practice: Principles and Guidelines (65), based on the principles of the International Conference on Harmonization guidelines on Good Clinical Practice (66) and the UK Policy Framework for Health and Social Care Research (67). ICNARC policies and procedures are based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

T4P will be conducted in accordance with the: terms of the favourable ethical opinion; the approved trial protocol; GCP guidelines; the UK Data Protection Act, UK General Data Protection Regulation; the Mental Capacity Act; and ICNARC CTU research policies and procedures.

18.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any additional patient facing material will be submitted to an appropriate Research Ethics Committee (REC), HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

T4P has received a favourable ethical opinion from the [South Central – Oxford C] Research Ethics Committee (Reference: 22/SC/0186) and approval from the Health Research Authority ((Integrated Research Application System (IRAS) number: 312405).

It is the responsibility of the site PI to obtain the necessary local approvals to run T4P at their site, including confirmation of capacity and capability. Evidence of confirmation of capacity and capability must be provided to the ICNARC CTU prior to site activation (*see section 9.2.1.3*).

18.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

18.5 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

18.6 Participant Confidentiality

Identifiable patient data, including full name, contact details, date of birth and NHS number will be required by the ICNARC CTU to successfully enable data linkage and follow-up participants. If informed consent cannot be obtained (e.g., for a participant who has died before regaining mental capacity), we will collect this data under the provisions of Section 251 of the National Health Service Act 2006 (subject to approval from the Confidentiality Advisory Group). The ICNARC CTU will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. We will seek consent to share the patients' anonymised data. All data will be stored securely. ICNARC is registered under the Data Protection Act (Registration number: Z6289325).

18.7 Expenses and Benefits

There will be no payments to participants for participation in this trial.

19 FINANCE AND INSURANCE

19.1 Funding

National Institute for Health Research (NIHR) – Health Technology Assessment Programme (HTA) (Project: NIHR131822).

19.2 Sponsorship and indemnity

University of Oxford are the Sponsor for T4P (reference: PID16200).

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

19.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

20 PUBLICATION POLICY

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 that the study was funded by NIHR-HTA. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

20.1 Dissemination

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 primarily for our participants
- Webinars and recorded interviews with researchers and PPI, available through our project 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 (55) 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
- Results synthesis to support incorporation into clinical guidelines
- Presentation slides and briefing papers for the study team to disseminate the research findings.

A Trial Report to the NIHR HTA Programme will present a detailed description of the trial and its results, along with recommendations for future policy, practice and research. 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.

20.2 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.

21 DEVELOPMENT OF A NEW PRODUCT / PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

22 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 the participating site for a minimum of 5 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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24 Appendix 1 – Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA#1	2.0	25.11.2022	Hayley Noble	• Clarifications made to inclusion criterion number 4 • Addition of APML to exclusion criteria • Minor update to exclusion criterion number 5 • Clarifications made to SAE severity classification and SAE reporting requirements to ICNARC CTU • Minor administrative updates

25 Appendix 2 – Expected adverse events

Expected SAEs that could be observed in participants up to critical care discharge following randomisation:

- *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 (definitions of these will in accordance with SHOT/SABRE guidelines).

If an SAE, as defined in Section 12.1, occurs this should be recorded and reported as described in Section 12.3.