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)

Statistical Analysis Plan Version 1.0

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Version	Date	Summary of main changes/justification	Timing
0.1	15/08/2024	First draft	Prior to first interim analysis data lock
0.2	05/09 2025	Bulk of revisions prior to first interim analysis	Prior to first interim analysis data lock
0.3	12/11/2025	Final outstanding comments and edits prior to finalisation	Prior to first interim analysis data lock
1.0	12/11/2025	First agreed version	Prior to first interim analysis data lock

Contents

1 Introduction

1.1 Background and rationale

United Kingdom (UK) blood services issued 294,055 platelet transfusions in 2024. After cancer services, critical care units use most platelets, for adults, children and infants/neonates. In most populations, including critical illness, platelet transfusions are mainly given to prevent spontaneous or procedure-induced bleeding in patients with low platelet counts (thrombocytopaenia).[1,2] However, recent randomised trials outside adult critical care show platelet transfusions may cause harm, including pre-term neonates and adult patients on anti-platelets medication presenting with intracerebral bleeding.[3,4] Recent systematic reviews by our group and others highlight a lack of evidence on safety and benefits of prophylactic platelet transfusions.[5,6] Clinical practice guidelines make general recommendations for restrictive platelet strategies, but are unable to recommend a platelet count below which giving platelets confers benefit rather than harm in adult critical care/ICU, so call for new research.[7–9] Typical trial designs for most platelet threshold randomised trials have compared two platelet count thresholds below which platelets are transfused (for example 10 vs 20 or 20 versus 50x10^9/L) and are unlikely to identify optimal thresholds.[10,11]

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) or time-defined (for example tracheostomy) interventions.[12–14]

The Threshold for Platelets (T4P) study is a prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure. The trial received favourable ethical opinion from the South Central – Oxford C Research Committee in UK and opened to recruitment on 27 September 2022.

Recruitment has now extended internationally (Republic of Ireland and Australia). The following document describes the proposed Statistical Analyses Plan (SAP) for the trial. The SAP is agreed in advance of analysing outcome data for the trial, so that data-derived decisions in the analyses are avoided. This SAP has been prepared in accordance with published guidelines.[15]

1.2 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.

1.3 Objectives and outcomes

- 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.

1.3.1 Primary Outcome – clinical effectiveness

- All-cause mortality at 90 days

1.3.2 Primary Outcomes – cost-effectiveness

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

1.3.3 Secondary Outcomes

- Mortality at discharge from critical care unit, hospital and at one year
- Survival to longest available follow-up
- Cumulative incidence of *major* and *fatal* bleeds classified according to the HEmorhage Measurement (HEME) bleeding score until critical care unit discharge[16]
- 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[17]
- Length of critical care unit and acute hospital stay
- Health-related quality of life (EQ-5D-5L questionnaire at 90 days and one year)[18]
- Resource use and costs at 90 days and one year
- Net monetary benefit (NMB) at one year

2 Methods

2.1 Trial 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 to <50x10^9/L).

2.2 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. Randomisation will be stratified by site.

The five platelet count randomisation thresholds are:

- <10x10^9/L
- <20x10^9/L
- <30x10^9/L
- <40x10^9/L
- <50x10^9/L

2.3 Sample size

The sample size was estimated from simulations across seven 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% to recommend an optimum threshold with a true mortality within 2% (in absolute value) of the optimum mortality value in each scenario. We increased the sample size to 2550 patients to allow for 6% refusal/withdrawal of consent post-randomisation (as in the "65" Trial).[19]

2.4 Framework

The primary outcome and specified secondary outcomes will be evaluated within an optimisation framework in which the principal outputs are not comparisons but statistical models for predicting average patient outcomes across the full (continuous) range of platelet count thresholds evaluated (threshold-response curves).

2.5 Statistical interim analysis and stopping criteria

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 for the primary outcome, to inform adaptation of the allocation ratio based on the posterior probabilities that each threshold has the lowest 90-day mortality of the randomised thresholds. Up to two outer thresholds (potentially at the same end of the spectrum) will be dropped if their posterior probability of having the lowest mortality is less than 1%. To avoid strongly unbalanced allocations, all remaining thresholds will have a minimum allocation percentage of half the equal randomisation rate (i.e. 10% if no thresholds are dropped, 12.5 % if 1 threshold is dropped and 16.7% if 2 arms are dropped). To avoid adapting on implausible or unlikely threshold-response curves, the algorithm will recommend equal allocation to remaining thresholds in the case of internal minimums in the posterior probability of a remaining allocated threshold being optimum (i.e. if probabilities are greater towards both limits of the range of remaining thresholds). 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.

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 (Data Monitoring & Ethics Committee) raises concerns about harms. Any decision to terminate the trial would be made by the TSC in conjunction with the trial funders.

2.6 Timing of final analysis

The end of the trial will be when all patients have completed their 90-day follow-up. Timing of the final analysis will depend partly on the acquisition of linked data for outcome assessment, following the end of the trial. Linkage to the audit databases (CMP, Irish National Intensive Care Unit Audit (INICUA), Scottish Intensive Care Society Audit Group (SICSAG), and Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS APD)) will be requested within 30 days after the date on which all patients (or, for interim analyses, the specified number of patients) have reached 90 days' follow-up. Patient identifiers will then be sent to NHS Digital for linkage to death registration records (for applicable countries). Within 15 days of receipt of the linked data from NHS Digital, audit database records will be re-extracted to incorporate any intervening updates, any patients remaining in follow-up (i.e. beyond 90 days) will be censored, the trial database will be locked, and the final analysis conducted.

2.7 Timing of outcome assessments

Following randomisation, interventions and procedures are recorded daily until discharge from critical care.

Other outcomes are collected at discharge from critical care (mortality, length of stay), and at ultimate discharge from acute hospital (mortality, length of stay).

Cumulative incidence of *major* and *fatal* bleeds are recorded until critical care discharge.

Venous and arterial thromboses are recorded until acute hospital discharge and at one year.

Duration of renal, advanced cardiovascular and advanced respiratory support are recorded until ultimate critical care unit discharge.

Serious adverse events are collected from randomisation until critical care unit discharge.

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 90 days and one year, surviving, consenting patients will be asked to complete an EQ-5D-5L questionnaire to assess their health-related quality of life and a health services questionnaire to assess their health service use.

3 Statistical Principles

3.1 Credible intervals and optimum

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 or mean of the respective outcome at all thresholds across the full range of investigated thresholds, each with a corresponding 95% credible interval. If the estimated threshold-response 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 steeper threshold-response curve would imply a stronger benefit or harm and a narrower region within which clinical judgement should be exercised, and a flatter curve would indicate smaller impacts of transfusion on outcome. If the threshold-response curve contains an internal optimum, then that optimum corresponds to the platelet count below which transfusion is expected to be beneficial and above which transfusion is expected to be harmful (alternatively, the point at which the estimated treatment effect is nil). An estimated optimum at the $<10x10^9$/L threshold would correspond to expected benefit across the whole range and an estimated optimum at the $<50x10^9$/L threshold would correspond to expected harm across the range. 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).

3.2 Adherence and protocol deviations

3.2.1 Exposure

Patients will be randomised to one of five equally spaced platelet thresholds (<10 to $<50x10^9$/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 until critical care unit discharge (i.e. all low bleeding risk procedures for which the patient's most recent platelet count is below their allocated threshold). If a patient is readmitted to the participating critical care unit during the index hospital stay within 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.

3.2.2 Protocol adherence

The number and percentage of patients found to have been ineligible following randomisation will be reported in each treatment group, together with the reasons for ineligibility (inclusion criteria not met or exclusion criteria met). These patients will still be used in the analysis.

Adherence to the trial protocol will be assessed by comparing, for each threshold, both the proportion of patients whose platelet count was below their assigned threshold prior to a specified procedure and (correctly) received a platelet transfusion before the procedure, and the proportion whose platelet count was above their threshold prior to a specified 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, distinguishing between the proportion of patients and events as appropriate.

Protocol deviations will be defined as:

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

The number and percentage of patients with at least one protocol deviation in each threshold group will be reported for initial procedures, and the number and percentage of patients and procedures for subsequent procedures.

3.3 Analysis Population

All analyses will adhere to the intention-to-treat principle. Patients will be analysed according to their initial assigned platelet threshold, irrespective of whether this was respected. All patients for whom the primary outcome is known will be included in the analysis, regardless of protocol adherence.

4 Trial population

4.1 Screening data

Screening logs will be used to record all patients with a platelet count $<50x10^9$/L who are admitted or accepted for admittance to critical care.

A CONSORT flow diagram will be used to summarise the number of patients who were:[20]

- Assessed for eligibility at screening
- Eligible at screening
- Ineligible at screening (with reasons)
- Eligible and randomised

- Eligible but not randomised (with reasons)

Additionally, the following more detailed summaries will be presented:

- Number and percentage of screened patients who did not meet inclusion criteria, overall and by criteria.
- Of the patients who met the inclusion criteria, number and percentage who met exclusion criteria, overall and by criteria.
- Of the eligible patients (i.e. met inclusion criteria and did not meet exclusion criteria), number and percentage not randomised, overall and by reason (if known).

4.2 Eligibility

4.2.1 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)[21]
- 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

4.2.2 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 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.

4.3 Recruitment

The CONSORT flow diagram will also be used to summarise the number of patients who were:

- Lost to follow-up (with reasons).
- Included in the primary analysis.
- Excluded from the primary analysis (with reasons).

4.4 Consent

A full description of the consent process is given in country-specific trial protocols and protocol appendices.

In the United Kingdom and Republic of Ireland, patients and/or a person consenting on behalf of the patient (e.g., family, friend, independent clinician) are asked for their consent for (a) continued participation and data collection, (b) receipt of a follow-up questionnaire (optional), (c) receipt of summary of trial results (optional), and (d) contact for future research (optional).

In Australia, patients are enrolled into the trial with a waiver of consent. Patients and/or a person consenting on behalf of the patient are approached for their consent to continue, or, notified of their involvement with an opportunity to opt-out of further data collection.

Where participants have favourable consent (or no response to opt-out in Australia) for continued participation and data collection, the full complement of trial data will be available for analysis.

There are certain scenarios where explicit consent may not be in place. These are:

a) Where the patient was discharged with capacity prior to consent being obtained, a telephone mechanism is in place to obtain consent. If telephone contacts were unsuccessful, the patient will be notified by post of their involvement and that their data will be included in the trial.
b) Where the patient passed away shortly after randomisation or was discharged from hospital without regaining capacity, before any consent could be obtained.

In these scenarios where no consent is in place, the following data will be available for analysis:

a) Patients in England
    - If no National Data Opt-Out (NDOO) in place - full complement of trial data available. For these patients in England, identifiable data collection to enable linkage to NHS databases is permitted under section 251 of the NHS Act 2006, following approval from the Confidentiality Advisory Group (CAG).

- If a NDOO is in place – only pseudonymised trial data available. Identifiable data is not permitted to be processed in this scenario, which will prevent obtaining any data via linkage.

b) Patients in Wales - full complement of trial data available. Identifiable data collection to enable linkage to NHS databases is permitted in these patients under section 251 of the NHS Act 2006, following approval from the CAG.
c) Patients in Northern Ireland - only pseudonymised trial data available, which will prevent obtaining any data via linkage.
d) Patients in Republic of Ireland – only pseudonymised trial data available, which will prevent obtaining any data via linkage.
e) Patients in Australia – only pseudonymised trial data available.

4.5 Withdrawal/follow-up

The number and percentage of patients (or a person consenting on behalf of the patient) who refuse or withdraw consent to trial participation will be reported in each group, with reasons where provided. For patients recruited in the United Kingdon or Australia, data collected up until the point of refusal/withdrawal will be included in the analysis, but no further data will be collected for that patient, with the exception of pseudonymised primary outcome unless they specifically requested that all data be removed (a full data refusal). For patients recruited in the Republic of Ireland, data will only be available on randomisation for such patients (they are treated the same as a full data refusal).

The total lost to follow-up for the primary outcome will include both consented patients for whom data is unavailable (true loss to follow-up), and those who withdrew from the study completely and requested that all data be removed.

The total lost to follow-up for secondary outcomes will include consented patients for whom data is unavailable (true loss to follow-up) and all patients who declined or withdrew consent for continued participation (regardless of request for removal of all data). The baseline characteristics (as described in Section 4.6) of patients completing a follow-up questionnaire at each time point will be compared with those of patients known to be alive at that time point who did not complete a follow-up questionnaire. The same approach will be taken for one-year questionnaires (noting that one-year follow-up is curtailed).

The number and percentage of patients lost to follow-up for questionnaire outcomes at 90 days and one year will be reported in each group.

4.6 Baseline patient characteristics

To maximise efficiency, trial data collection will be nested within the national clinical audit databases, besides the Case Report Form (CRF).[22] The following baseline demographic and clinical data will be summarised by allocated treatment group, (using mean, standard deviation (SD) and median (lower quartile, upper quartile) for continuous variables, or counts and percentages (%) for binary and categorical variables), but not subjected to statistical testing:

- Demographics:
  - From CRF or audit databases:
    - Age – median (lower quartile, upper quartile)
    - Sex (male, female) – number (%)
    - Ethnic group (White, Asian, Black, Mixed, Other or not stated) – number (%)

- Past medical history:
  - From CRF or audit databases:
    - Body mass index categories (<18.5, 18.5–<25, 25–<30, 30–<40, ≥40) – number (%)
    - Prior hospital length of stay – mean (SD), median (lower quartile, upper quartile)
- Current/suspected diagnoses at randomisation:
  - From CRF or audit databases (as described in Section 5.3.1):
    - Bone marrow failure – number (%)
    - Liver disease – number (%)
    - Sepsis – number (%)
    - None of the above – number (%)
- Physiology at randomisation:
  - From CRF:
    - Latest platelet count –median (lower quartile, upper quartile)
    - Platelet transfusion prior to randomisation – number (%)
    - Anti-platelet therapies prior to randomisation – number (%)
- Acute severity of illness from first 24 hours following admission to the unit:
  - From CRF or audit databases:
    - $ICNARC_{H\text{-}2023}$ model predicted risk of death – mean (SD)
    - APACHE II score – median (lower quartile, upper quartile)

5 Clinical Effectiveness Analysis

5.1 Primary clinical outcome

The primary clinical outcome is 90-day mortality, defined as death due to any cause by 90 days following randomisation.

Date of death will be collected directly from the sites, supplemented by linkage to routine data sources. Where data are discrepant between sources, quality assurance checks will be conducted with sites and the site data considered paramount. Where sites are unable to validate discrepancies in linked records, deaths identified by either linked data source will be considered true, with CRF data taking priority in cases of discrepant dates. Where patients have refused consent for continued participation, 90-day mortality will be collected directly from sites.

5.2 Secondary clinical outcomes

5.2.1 Mortality at discharge from critical care unit and acute hospital

Patient outcome (alive/dead) at discharge from ICU and acute hospital are recorded as part of routine data collection and will be collected from linked audit databases records, supplemented by data recorded on the CRF. Mortality at discharge from the critical care unit will be defined as death due to any cause before discharge to any location providing a level of care less than Level 2 (high dependency care). Mortality at discharge from acute hospital will be defined as death due to any cause before discharge from acute hospital. Patients transferred from the original acute hospital to another acute hospital will be followed up until they leave acute hospital. ICU and hospital mortality will be censored at 90 days.

5.2.2 Mortality at one year and to longest available follow-up

Mortality at one year will be defined as death due to any cause by one year following randomisation, and otherwise derived as per mortality at 90 days. Since the trial ends when the final patient reaches 90 days, some patients will not reach 1 year follow-up and will be excluded from analysis of this outcome. Mortality occurring after discharge from acute hospital until longest available follow-up will be collected by data linkage to routine data sources.

5.2.3 Major and fatal bleeds

Major and fatal bleeds are classified according to the HEME bleeding score and are collected directly from sites until critical care discharge.

5.2.4 Venous and arterial thromboses in hospital and to one year

Venous and arterial thrombosis occurrences in hospital and to one year are collected by data linkage to NHS Digital from the NICE-mandated hospital-acquired venous thromboembolism (VTE) audit (also known as hospital-acquired or hospital-associated thrombosis (HAT)) until acute hospital discharge and at one year, supplemented by data collected directly from sites and patient questionnaires where necessary, and from patient questionnaires at 90 days and one year.[23]

5.2.5 Duration of renal, advanced cardiovascular and advanced respiratory support

Duration of renal, advanced cardiovascular and advanced respiratory support are defined according to UK CCMDS criteria and are recorded as part of routine data collection and will be collected from linked audit databases records, supplemented by data collected directly from sites where necessary, up to ultimate discharge from critical care.

5.2.6 Length of critical care unit and acute hospital stay

Duration of ICU and acute hospital stay will be derived from linked audit databases records, supplemented by data collected directly from sites where necessary. Duration of critical care unit stay will be calculated as the sum of the duration (in linear time) from the date and time of randomisation to the date and time of first discharge from the critical care unit or death in the critical care unit, plus the duration of any subsequent admissions to the critical care unit within the same acute hospital stay.

Duration of acute hospital stay will be calculated as the duration in calendar days (as times of hospital admission and discharge will not be available) from the date of randomisation to the date of acute hospital discharge or death in acute hospital.

5.3 Clinical effectiveness analysis methods

5.3.1 Primary outcome

The estimand of interest is the threshold leading to the maximum probability of survival (or minimum expected 90-day all-cause mortality).

Phrased in terms of the components of an estimand, the **treatment** is the threshold assigned at randomisation, the analysis **population** is all patients enrolled in the trial who do not withdraw completely; the **endpoint** is 90-day all-cause mortality (as described in Section 1.3.1); the **summary measure** is the median of the posterior distribution of the threshold associated with the minimum 90-day all-cause mortality; and a “treatment policy” strategy will be used to address protocol non-adherence (the only anticipated **intercurrent event**).[24]

The primary outcome will be modelled using logistic regression with a Gaussian process (GP) to allow a flexible threshold-response curve to be fitted.[25] This GP provides a non-parametric regression

method and will have two components: a squared exponential (SE) kernel multiplied by a linear kernel. A GP assumes a multivariate Gaussian joint distribution of functions, and requires a prior distribution over functions, which can be defined by a mean function and a covariance function (the kernel). The covariance function will be constructed by multiplying an exponential part with a linear part

$$K_{GP}(x, x') = K_{SE}(x, x') \times \sigma^2 x x'$$

where x represents the transfusion threshold, $K_{SE}(x, x') = \alpha^2 \exp\left(-\frac{1}{2p^2}(x - x')^2\right)$ is the SE part, and $\sigma^2 x x'$ the linear part.

For the SE kernel, ρ is the length scale and α is the marginal standard deviation (controls the magnitude of the range of the function represented by the GP). For these parameters we define the following prior distributions : $\rho \sim IG(12,21)$ (inverse gamma (IG) distribution such that 1% of its distribution is < 1 and 1% of its distribution is > 4), and $\alpha \sim N(0,0.2)$, where 0.2 is the standard deviation. For the linear kernel, the prior will be defined as $\sigma^2 \sim IG(5,5)$. The observed and predicted thresholds will be scaled (divided by 10) and centred.

The model will be adjusted for the randomisation stratification variable (random effect of site) using country specific non-centred random effects.

Variation in the threshold-response curve shape and optimum threshold location in pre-defined patient subgroups will be evaluated by expanding the primary analysis model to allow independent threshold-response curves to be fitted for each subgroup. We will undertake pre-determined analyses, where numbers are sufficient, of patient groups with:

- Underlying bone marrow failure (defined as a white cell count <1.0x10^9/L with an explanatory underlying diagnosis, e.g. haematological malignancy, receiving chemotherapy).
- Underlying liver disease (defined as acute hepatic failure as a reason for critical care unit admission or severe chronic liver disease - cirrhosis, portal hypertension or hepatic encephalopathy).
- Sepsis (defined according to Sepsis-3 criteria).[26]

The results of subgroup analyses will be interpreted taking into account accepted criteria for credible subgroup effects.

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 country-specific probability of mortality at all thresholds across the full range of investigated thresholds, each with a corresponding 95% credible interval.

We will fit the models using Markov Chain Monte Carlo (MCMC) methods, via the Stan software[27] for Bayesian data analysis. Multiple chains will be run, initialised with diffuse starting values, to achieve an effective sample size of at least 10,000 for all quantities of interest for posterior inference.

We will explore alternative ways of presenting supplementary results to facilitate interpretation, such as comparisons between thresholds, estimated effects of changes in threshold on patients impacted, and estimated effects of transfusion conditional on platelet count, derived from outputs of the primary analysis model and data collected on platelet counts, transfusions and procedures.

For example, from the primary outcome model, we can derive survival probability curves as a function of platelet count for patients allocated to a lower threshold (receiving a platelet transfusion) and higher threshold (not receiving a platelet transfusion):

$$st_p = s_p + x_p \cdot (1 - r_p) \text{ [transfused patients]}$$

$$sn_p = s_p - x_p \cdot r_p, \text{ [not transfused patients]}$$

where r_p and s_p are the observed proportion of patients allocated to a lower threshold (transfused) and the observed overall survival probability at platelet count p respectively, and x_p is the effect of receiving a platelet transfusion, defined as

$$x_p = \frac{(y_{p+1} - y_p)}{e_p},$$

where y_p and e_p are the estimated survival probability at threshold p (from the fitted threshold-response curve) and the observed proportion of patients at platelet count p.

5.3.2 Secondary outcomes

The threshold-response curve for the secondary outcomes will be fitted using a GP model with an SE × linear kernel analogous to the primary outcome model.

The binary secondary outcomes (mortality at discharge from critical care unit, hospital, and at one year, major and fatal bleeds, and venous and arterial thromboses in hospital and to one year) will be reported by treatment group using numbers and percentages. They will be analysed using logistic regression models.

The continuous secondary outcomes (duration of renal, advanced cardiovascular and advanced respiratory support, and length of critical care unit and acute hospital stay) will be reported as the mean (SD) and median (lower quartile, upper quartile) by treatment group, overall and stratified by survival status to discharge. Secondary outcomes will not be modelled for interim analyses. The performance of different models for continuous and ordinal outcomes (linear, Gamma, negative binomial, and ordered logistic) will be compared using simulated outcome data and specified in an updated SAP prior to locking data for the final analysis.

Survival to longest available follow-up will be presented as a Kaplan-Meier plot by treatment group.

All adjusted analysis will include the random effect previously listed in section 5.3.1.

We will provide supplementary descriptive analysis (without formal testing of comparisons) of bleeding episodes (e.g. location and severity of bleed) in each allocated threshold.

5.3.3 Model diagnostic procedures

We will check that the Markov chains have converged to their posterior distributions through inspection of the chains and the potential scale reduction statistic ($\hat{R}$). If the chains are not stable and overlapping, or $\hat{R}$> 1.05 for any parameter of interest, additional iterations will be run until equilibrium is achieved. For models run using the Stan software, Hamiltonian Monte Carlo (HMC) specific diagnostics will also be checked. Additionally, we will explore model fit and prior sensitivity.

Where non-convergence or other modelling problems are identified, the causes of the problem will be investigated by constructing and evaluating simpler models. Where data sparsity is identified as the issue, the model may be simplified, for example by combining parameters. Reparameterisations

or alternative priors may also be considered. The DMEC will be informed of any problems and the action taken to resolve these issues.

6 Cost-effectiveness analysis

6.1 Primary economic evaluation outcomes

The primary economic evaluation outcomes are the incremental costs, QALYs and net monetary benefit at 90 days.

6.2 Secondary economic evaluation outcomes

The secondary cost-effectiveness outcomes are:

- 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

6.3 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 audit databases and HES for efficiency.

Categories of resource use where differences, according to the platelet threshold, may be anticipated to drive incremental costs will be measured, 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. Readmissions to critical care will be accessed from the audit databases, 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 and for hospital outpatient visits and community service use from a recommended published source. 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, successfully used to assess patient-reported health status in previous critical care unit trials.[28] 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, 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.

NMB at one year will be calculated 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 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. 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.

6.3.1 Sensitivity analysis for cost-effectiveness

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).

7 Handling of missing data

We will handle missing data appropriately within the Bayesian paradigm, adding imputation sub-models for missing covariates if required. 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. 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 (audit databases 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.

The amount of missing clinical primary outcome data is anticipated to be minimal and will be accounted for in a sensitivity analysis. Subgroup analyses will be restricted to patients with complete data. Missing data in costs and HrQoL will be handled appropriately within the Bayesian paradigm.

8 Safety

Expected Serious Adverse Events (SAEs) (serious transfusion related adverse reactions which relate to the administration of the platelet transfusion) and any other possibly related SAEs, will be recorded for all randomised patients from the time of randomisation up to critical care discharge.

The total number of patients experiencing one or more serious adverse event from randomisation until critical care discharge will be compared between groups using Fisher’s exact test. The numbers of serious adverse events, and the counts and percentages of patients experiencing serious adverse events, overall and by type, will be presented by allocated treatment group.

9 Statistical software

All analyses will be conducted in Stata, R, and the Stan software (in the available versions at the time of analyses).[27,29,30]

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