Threshold for Platelets (T4P):

A prospective randomised trial to define the platelet count below which critically ill patients should receive a platelet transfusion prior to an invasive procedure.

Overview

Background and rationale

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

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

Typical trial designs, comparing two maximally separated thresholds (for example 20 versus 50 x10^9/L) 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) or time-defined (for example tracheostomy) interventions.

Aim

To define the optimum platelet threshold below which platelets should be transfused prior to a low bleeding risk invasive procedure in critically ill patients and to explore whether the optimum threshold differs according to patient characteristics.

Design

T4P is an open label, randomised, Bayesian adaptive, comparative effectiveness trial, across five equally spaced platelet count thresholds.

Objectives

Primary 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.

Secondary Objectives:

- 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

Site eligibility

- UK NHS hospitals containing a Critical Care Unit
- Active participation in Case Mix Programme (CMP)
- Identify a Principal Investigator (PI) to lead the T4P trial locally
- If possible, appoint an Associate/Sub PI to assist the PI with the running of the T4P trial locally
- Identify a T4P Research Nurse (funding available – see below)
- Agree to incorporate the T4P Trial into routine unit activity – particularly highlighting the importance of systematic screening for potential eligible patients, clinical equipoise between all threshold groups, and prompt randomisation
- Agree to adhere to randomisation allocation and ensure adherence to the protocol
- Agree, where possible, to recruit all eligible patients and maintain a Screening Log
- Agree to data collection requirements

Patient eligibility

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.

Sample size

The sample size is 2550 patients.
These will be recruited from 66 participating NHS hospitals containing a Critical Care Unit within the Case Mix Programme.

Randomisation

Patients will be randomised to one of five platelet thresholds using a deferred consent model:

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

Clinical equipoise must exist for randomisation to all the above thresholds. A central web-based randomisation service will be used.

Intervention group:
One of five equally spaced platelet thresholds (<10 - <50x10^9/L), below which the patient would receive a single adult equivalent dose (AED, defined according to national specifications) of platelet transfusion delivered before or during the procedure. The patient should not receive a platelet transfusion if the platelet count prior to the procedure is above the allocated threshold.

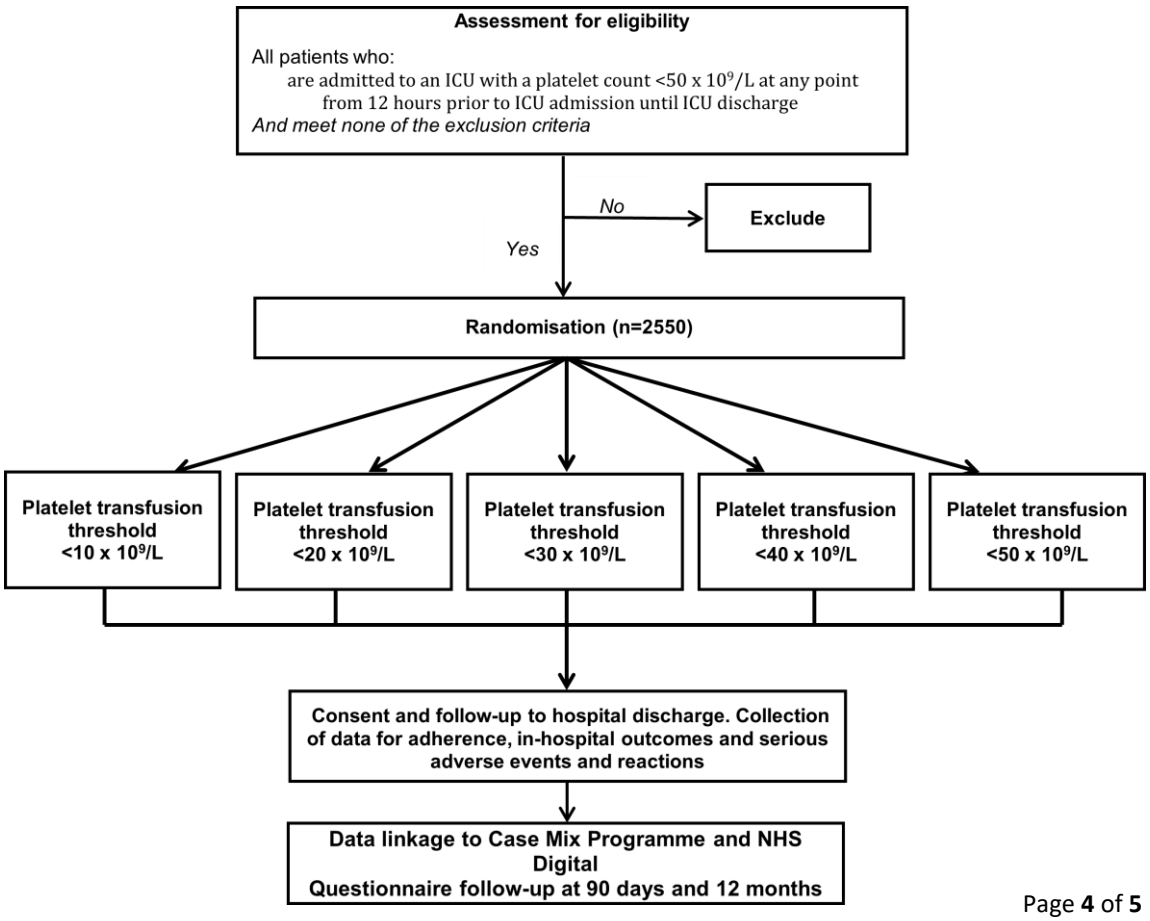
Treatment according to the randomly allocated threshold will continue for all subsequent low bleeding risk invasive procedures meeting the definition for inclusion, or those deemed as low bleeding risk by the treating clinician, until critical care unit discharge.

Consent

T4P will adopt 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.

Consent will be obtained from patients once they have stabilised and are deemed to have capacity. In the interim, the site research team will approach a Personal Consultee (in person or via telephone) and/or Nominated Consultee, 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.

Trial flow



Trial management and investigator team

Chief Investigator	Professor Peter Watkinson, University of Oxford
Co-Investigators	Dr Akshay Shah, University of Oxford Professor Simon Stanworth, University of Oxford Professor Duncan Young, University of Oxford Professor Tim Walsh, University of Edinburgh Dr Matteo Quartagno, UCL Professor Richard Grieve, LSTHM Dr Alexina Mason, LSTHM Professor David Harrison, ICNARC Dr James Doidge, ICNARC Mr Paul Mouncey, ICNARC Dr Doug Gould, ICNARC
Trial Management	ICNARC Clinical Trials Unit
Trial Manager	Hayley Noble
Trial Statistician	Professor David Harrison, Dr James Doidge, Dr Alexina Mason

Funding and resources

This trial is funded by the National Institute for Health Research (NIHR) – Health Technology Assessment (HTA) Programme (NIHR ID 131822).

There will be data for T4P sourced from the Case Mix Programme or from NHS Digital via data linkage (e.g., longer-term mortality and subsequent healthcare utilization).

Direct research costs – from ICNARC

- £250 start-up & first patient, £250 close-down and £175 per patient

Advised NHS support costs – from LCRN

The T4P Trial has been adopted onto the NIHR Portfolio (CPMS ID: 53274).