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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

Education Webinar

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Chief Investigator: Prof Peter Watkinson

Introductions -

- Chief Investigator
  - Prof Peter Watkinson
- Co-Investigators
  - Prof Simon Stanworth
  - Dr Akshay Shah
  - Joanna Calder (PPI)
- ICNARC CTU
  - Hayley Noble (Trial Manager)
  - Julie Camsooksai (Clinical Research Assistant)

The problem: prophylactic platelet transfusions

- Thrombocytopenia is common in ICU patients (<50x10^9/L): 5-20%
- Multifactorial aetiology (sepsis, liver failure, cancer)
- ~ 9% will receive a platelet transfusion – mainly for prophylaxis
- 2nd biggest user of platelets (after cancer services)
- No high-quality data to inform this practice!
- Evidence from non-ICU patients (PATCH, PLaNET-2) suggests harm

Curley A, Stanworth SJ et al. NEJM 2019; 380: 242-51
Stanworth S et al. Transfusion 2013; 53: 1050-8
Greinacher A et al. Blood 2016; 128: 3032

What are the issues?

- Platelet count is a poor predictor of bleeding
- Assumption that transfusion will consistently raise platelet counts
  - Modified by transfusion factors - storage age, ABO-matching
  - Patient factors – underlying illness (sepsis, cancer)
- Other effects of platelets – immunomodulation
- Bleeding rates are low (0.1-3%) -> appropriate outcome measure?

Arnold DM et al. Res Pract Thromb Haemost 2017; 1: 103-11
Gottschall J et al. Transfusion 2020; 60: 46
Shah A et et al. Transfus Med 2020; 30: 515-17
Aubron C et al. Crit Care 2018; 22: 185
Warner MA et al, Anesth Analg 2019l 128: 288-95

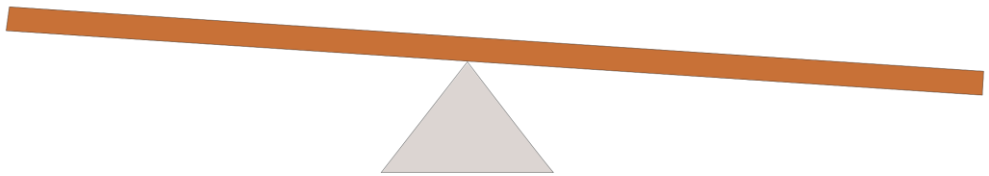
Uncertainties between benefits and risks

Benefits

- Haemostasis
- Certain subgroups may benefit e.g. trauma, marrow failure

Risks

- Increased mortality (critically ill neonates, intracranial bleed)
- Worse organ failure
- Transfusion reactions (x2 common with platelets)



Neonates: Primary outcome

	<25 (n=331)	<50 (n=329)	Odds ratio (95% CI)	p-value
Major/severe bleed or mortality by day 28	61/329 (19%)	85/324 (26%)	**1.57 (1.06 - 2.32)†**	0.02

Number needed to harm = 100/(26-19) = 14.3

For every 14.3 patients treated with <50 strategy, 1 extra MB or death would be expected

† Adjusted for gestational age, presence of IUGR and centre

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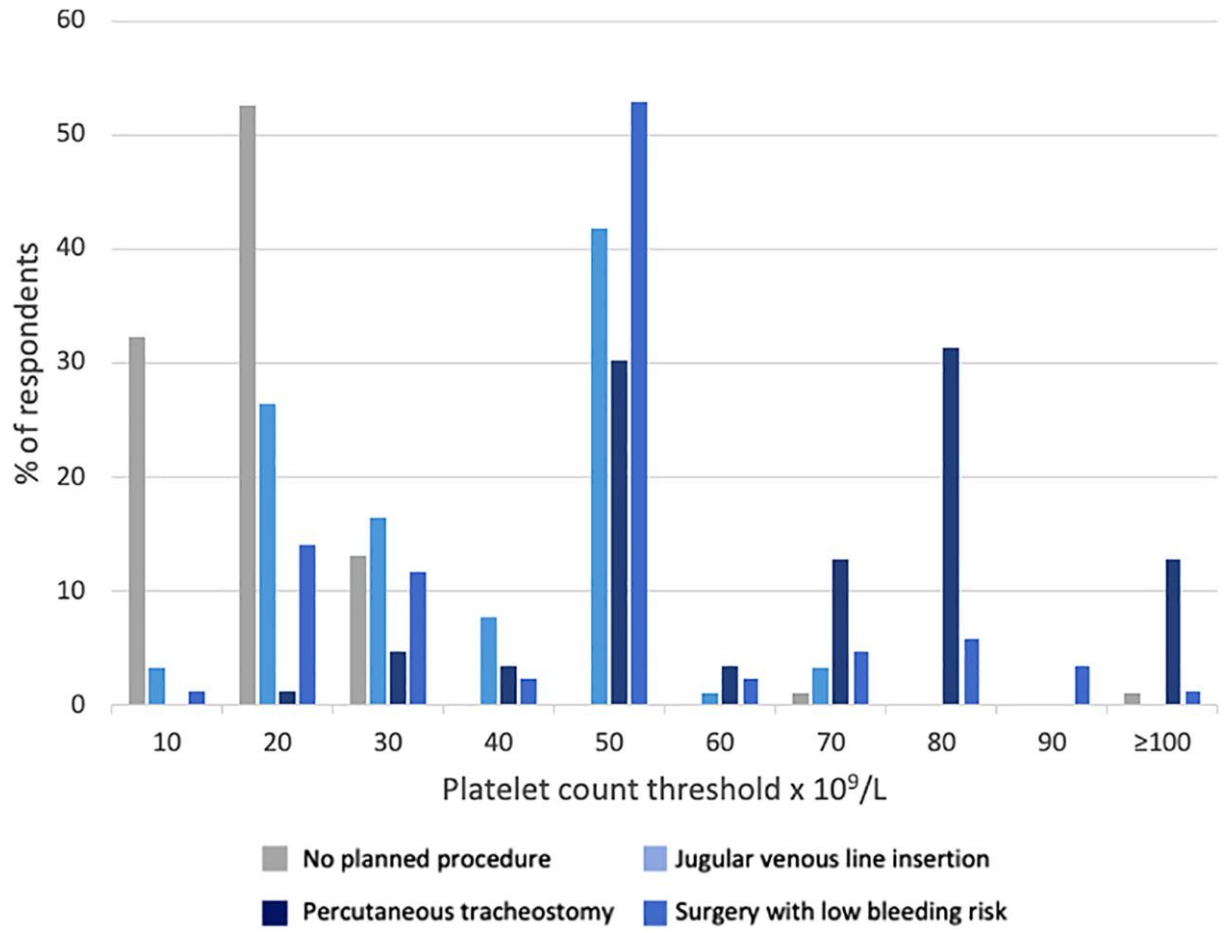
Inconsistent guideline recommendations

Guideline group	Recommendation	Strength of recommendation	Quality of evidence
European Society of Intensive Care Medicine 2020	We suggest not using platelet transfusion to treat thrombocytopaenia unless the platelet count falls below 10 x 10^9/L	Conditional	Very low
	We make no recommendation regarding prophylactic platelet transfusion prior to invasive procedures for platelet counts between 10 and 50 x 10^9/L	Research recommendation	
Society of Interventional Radiology 2019	Consider platelet transfusion if platelet count is <20 x 10^9/L for bleeding risk procedures	Weak	Very low
British Society for Haematology 2017	Consider performing the following procedures above the platelet count threshold indicated: - Central venous lines >20 x 10^9/L (using ultrasound) - Major surgery >50 x 10^9/L - Lumbar puncture >40 x 10^9/L	Strong Strong Very weak	Moderate Low Low
	Give prophylactic platelet transfusions (platelet transfusions to patients who do not have clinically significant bleeding and do not require a procedure) to patients with reversible bone marrow failure (e.g. general critically ill) at or above 10 x 10^9/L	Strong	Moderate
	Consider increasing the threshold for prophylactic platelet transfusion to between 10 and 20 x10^9/L in patients judged to have additional risk factors for bleeding (e.g. sepsis)	Very weak	Low
American Association of Blood Banks (AABB) 2015	The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than 20 × 10^9/L	Weak	Low quality

Surveys demonstrate variation in practice



Transfusion Medicine, Volume: 30, Issue: 6, Pages: 515-517, First published: 12 October 2020, DOI: (10.1111/tme.12728)

Threshold for Platelets (T4P)

- 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
- Open label, randomised, Bayesian **adaptive**, comparative effectiveness trial across **five equally-spaced thresholds** of thrombocytopaenia:

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

- Primary outcome (clinical):
  - All-cause mortality at 90 days

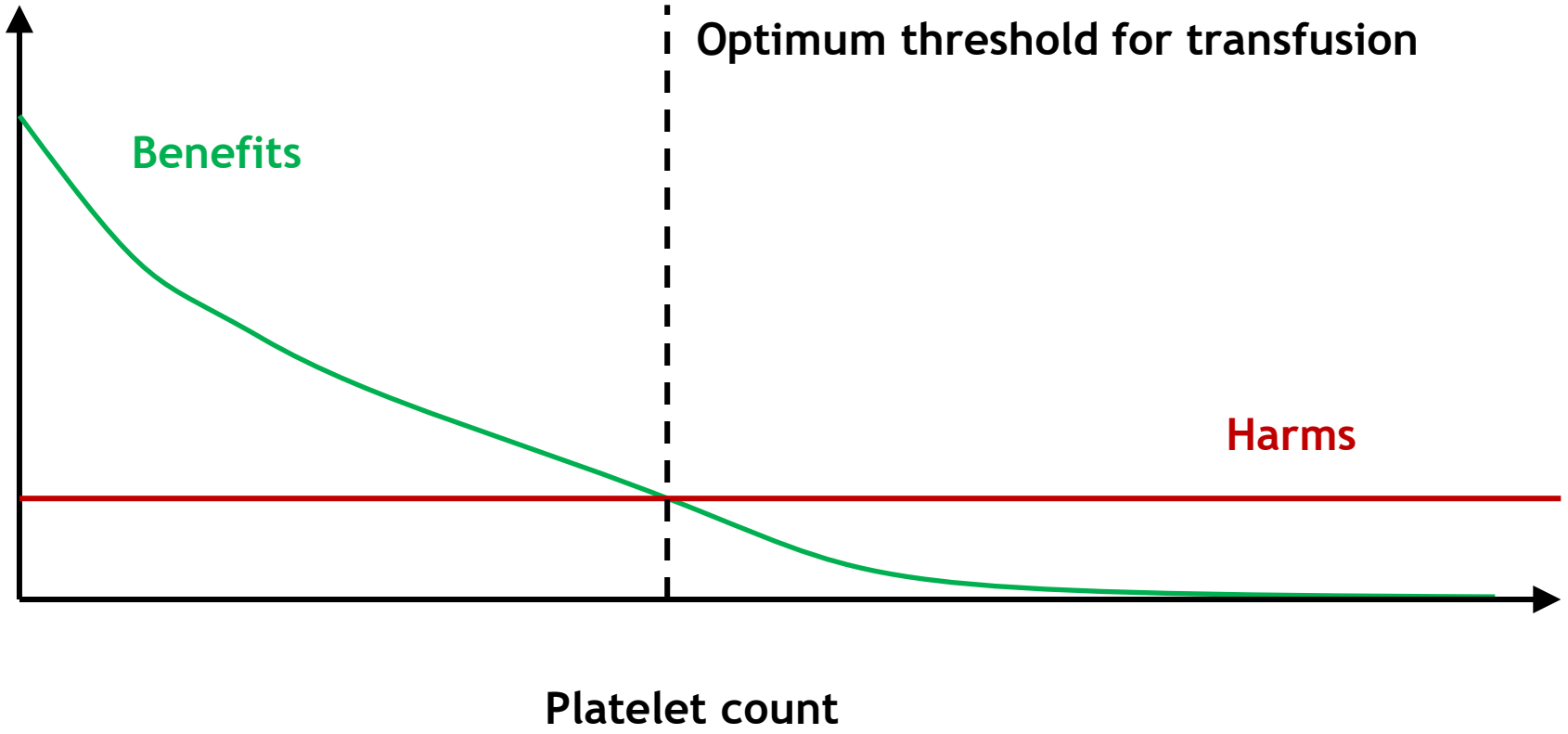
What is a threshold trial?

- Novel concept, related to a dose-finding study
  - Traditional trials seek to answer:
    - '*is treatment X more effective than treatment Y [or no treatment]?*'
    - Estimates the average effect among population/subgroup
  - In contrast, our threshold design seeks to answer:
    - '***in which patient subgroups***, *do the benefits of an effective treatment outweigh the risks?*'
    - Many potential applications in critical care decision making

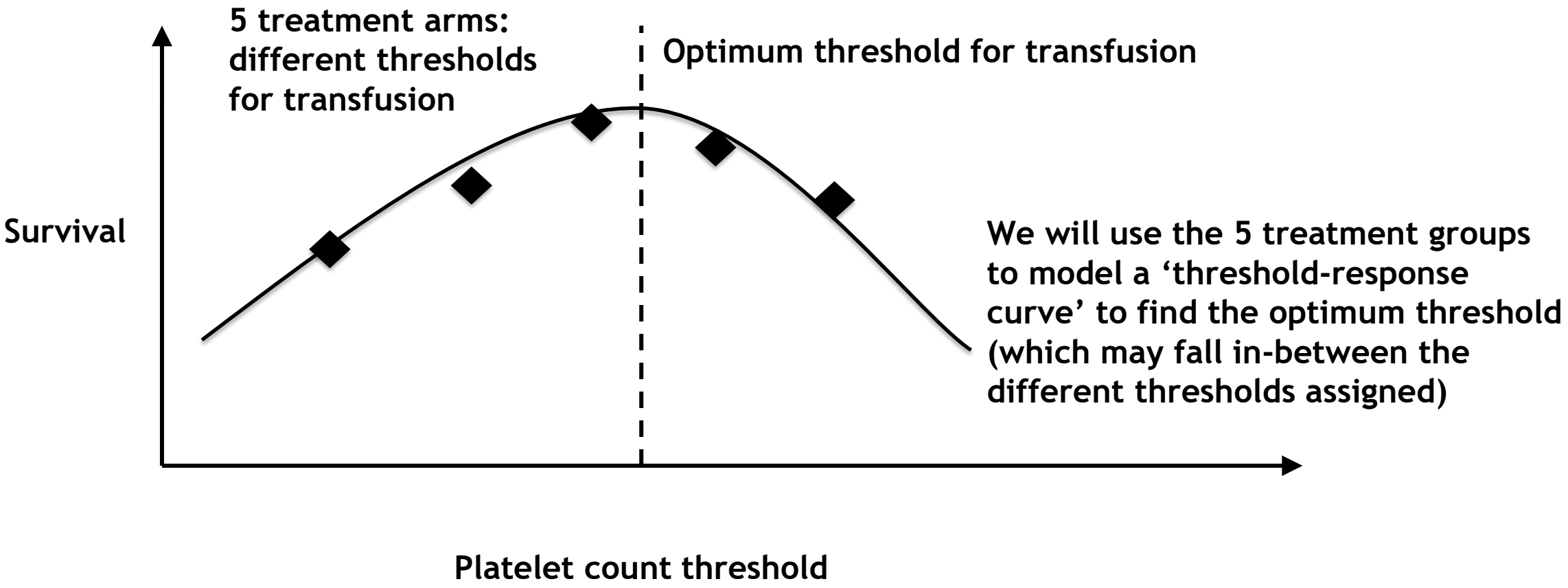
The platelet threshold problem

- Patients with low platelet counts may be at increased risk of bleeding associated with minor procedures
- Platelet transfusions may reduce that risk (benefit to patients) but can introduce other risks (e.g. infection, transfusion reaction, thrombus)
- Question: how low does a patient's platelet count need to be for the benefits of transfusion to outweigh the risks?
  - i.e. *which patients* (defined by their platelet count and planned procedure) can be expected to benefit from platelet transfusion?

Benefit vs risk of platelet transfusion



The threshold-response curve



Adaptive Randomisation: the idea

- Before running the trial we have equipoise
  - The probabilities that each of the 5 thresholds lead to the ‘best’ outcome are equal
- During the trial, we gain new information
  - So these probabilities can be updated using our statistical model
  - Some thresholds may now have higher probabilities of being ‘best’ than others
- Adaptive randomisation allows us to randomise more patients to the thresholds close to the ‘best’
  - By modifying the percentage of patients allocated to each threshold during the trial

T4P – Trial Overview

- 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. Platelet transfusion being considered for a *low bleeding risk invasive procedure**
     - Vascular catheter insertion and removal (central venous – 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:
       - Arterial catheter line insertion
       - Pleural drain
       - Interventional Radiology
       - Bronchoscopy with or without lavage
       - Wound dressing changes
       - Surgical procedures where the clinical team agree risk of bleeding is low, e.g. re-look laparotomy or wound closure

'Other' list is not exhaustive

T4P – Trial Overview

- 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. Advance decision refusing blood/blood component transfusions (e.g. Jehovah's Witnesses)
  5. Death perceived as imminent or admission for palliation.
  6. Previously randomised into T4P
  7. Fulfilled all the inclusion criteria and none of the other exclusion criteria ≥ 72 hours

T4P Trial Overview

- Screening
  - All patients 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**
- Randomisation
  - Web-based service, available 24/7
- Consent
  - Deferred consent model
  - Prospective consent is an option in rare case where patient has full mental capacity to provide fully informed consent

Summary

- Thrombocytopenia is a common problem in the ICU
- Prophylactic platelet transfusions are commonly prescribed in the absence of high-quality data
- However, platelet transfusions may be causing harm (as evidenced in other groups)
- There is variation in clinical practice and guidelines groups aren't sure what to recommend -> unmeasured harm
- T4P provides a unique opportunity to address this uncertainty once and for all
- The novel trial design may also be applicable to other clinical situations in critically ill patients