Comparison of different platelet transfusion thresholds prior to insertion of central lines in patients with thrombocytopenia (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of different platelet transfusion thresholds prior to the insertion of a central line in patients with thrombocytopenia (low platelet count).

BACKGROUND

Description of the condition

Patients with a low platelet count (thrombocytopenia) often require the insertion of central lines (central venous catheters (CVCs)). CVCs are catheters with tips that lie within the proximal third of the superior vena cava (large vein which returns blood to the heart), the right atrium or the inferior vena cava (Bishop 2007; Smith 2013). They can be inserted through a superficial vein (e.g. the basilic or cephalic veins in the arm) or a central vein (most commonly the jugular, subclavian or femoral veins) (Bishop 2007; Smith 2013). There are four main types: 1) a non-tunnelled line into a central vein (short-term use); 2) a line inserted into a superficial vein (medium-term use); 3) a tunnelled line (long-term use); and 4) a totally implanted device (long-term

use) (Bishop 2007; Smith 2013). They have a number of uses; these include: administration of chemotherapy and other irritant drugs with fewer complications; intensive monitoring and treatment of critically ill patients; administration of total parenteral nutrition; and long-term intermittent intravenous access for patients requiring repeated treatments (Smith 2013). Patients requiring CVCs can have a variety of conditions, and include: patients with haematological malignancies, patients receiving chemotherapy, patients with liver failure, and patients who are critically ill (Bishop 2007; Smith 2013).

CVCs are associated with complications, these include bleeding, thrombosis, infection, misplacement of the CVC and pneumothorax (Bishop 2007; Smith 2013).

A low platelet count is a relative contraindication to the insertion of a CVC due to the risk of bleeding (Bishop 2007; Smith 2013). Platelet transfusions are used in modern clinical practice to prevent

and treat bleeding in thrombocytopenic patients. Administration of platelet transfusions to patients with haematological disorders now constitute a significant proportion (up to 67%) of all platelet components issued (Cameron 2007; Greeno 2007; Pendry 2011), and 15% of these are given to prevent bleeding prior to a procedure (Estcourt 2012).

Central line insertion is the commonest intervention that requires prophylactic platelet transfusions (to prevent bleeding) in patients with haematological disorders (Estcourt 2012). Critically ill patients usually require central line insertion to administer treatments. A large United Kingdom (UK) study of patients admitted to the intensive care unit (ICU) reported that 9% developed thrombocytopenia (Stanworth 2013).

Description of the intervention

Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to CVC insertion (into internal jugular, femoral or subclavian veins), in order to mitigate the risk of serious peri- or post-procedural bleeding. The platelet count threshold recommended prior to CVC insertion varies significantly from country to country. For example, in the UK the current threshold is 50×10^9/L (BCSH 2003), in Belgium the threshold is 30×10^9/L (Bosly 2007), in the United States (US) the threshold is 20×10^9/L (Kaufman 2015), and in Germany the threshold is 10×10^9/L (GMA 2009).

There is therefore no standard platelet count that alternative thresholds can be compared against. Therefore we will make the following two main comparisons.

1. The commonest thresholds recommended by guidelines from different countries (10×10^9/L, 20×10^9/L, 30×10^9/L, 50×10^9/L) versus no prophylactic platelet transfusion prior to the procedure.

2. The lower thresholds recommended by guidelines from different countries (10×10^9/L, 20×10^9/L, 30×10^9/L) versus the highest commonly used threshold (50×10^9/L).

Platelet transfusions are associated with adverse events. Mild to moderate reactions to platelet transfusions include rigors, fever, and urticaria (an allergic reaction) (Heddle 2009). These reactions are not life-threatening but can be extremely distressing for the patient. Rarer, but more serious sequelae include: anaphylaxis (life-threatening allergic reaction); transfusion-transmitted infections; transfusion-related acute lung injury; and immunomodulatory effects (Benson 2009; Blumberg 2009; Bolton-Maggs 2012; Heddle 2009; Khan 2007; Taylor 2010; Knowles 2011; Pearce 2011; Popovsky 1985; Silliman 2003). The requirement to administer platelet transfusions to correct thrombocytopenia prior to central line insertion may additionally delay the start of treatments, which may be time-critical in a patient in intensive care. It remains unclear whether platelet transfusions in thrombocytopenic non-bleeding patients, despite improving the platelet count, reduces the incidence of clinically important bleeding or improves other meaningful patient-oriented outcomes, such as mortality.

How the intervention might work

Platelet transfusions are administered to thrombocytopenic patients in order to increase the platelet count and therefore reduce the incidence of bleeding. However, the risk of bleeding after a central line insertion appears to be low if an ultrasound-guided technique is used (Cavanna 2010; Hind 2003). A systematic review showed that ultrasound guidance significantly reduced the failure rate of cannulating the internal jugular vein (risk ratio (RR) 0.14, 95% confidence interval (CI) 0.06 to 0.33) compared to using an anatomical landmark method (Hind 2003). In Cavanna 2010 1978 ultrasound-guided CVC procedures were performed in 1660 patients who had a solid or haematological malignancy, of which 116 had a platelet count below 50×10^9/L, and 70 had a platelet count below 20×10^9/L. None of the patients experienced major bleeding. Patients may therefore be exposed to the risks of a platelet transfusion without any obvious clinical benefit.

Why it is important to do this review

As discussed above, the platelet count threshold recommended prior to CVC insertion varies significantly from country to country (BCSH 2003; Bosly 2007; GMA 2009; Kaufman 2015). This indicates significant uncertainty by clinicians of the correct management for these patients.

Several non-randomised studies have demonstrated the safety of performing invasive procedures without clinically significant bleeding in patients with thrombocytopenia who did not receive prophylactic platelet transfusions (Foster 1992; Haas 2010; Hong Pheng Loh 2007; Ray 1997). The use of a platelet count threshold above which a platelet transfusion is required prior to CVC insertion has therefore been called into question. It is uncertain whether platelet transfusions are effective at preventing bleeding in patients with thrombocytopenia undergoing an invasive procedure. If effective, the platelet count threshold above which platelet transfusions are clinically effective is also uncertain.

O B J E C T I V E S

To assess the effects of different platelet transfusion thresholds prior to the insertion of a central line in patients with thrombocytopenia (low platelet count).

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials (RCTs), irrespective of publication status.

Types of participants

We will include patients of any age with thrombocytopenia (as defined by the studies' own definitions) requiring insertion of a central venous catheter (CVC) (tunnelled or untunnelled), or portacath. We will exclude patients who are experiencing clinically significant bleeding at the time of the catheter insertion because such patients are routinely given platelet transfusions to treat the bleeding.

Types of interventions

We will include RCTs comparing the following two types of platelet transfusion regimes.

1) No platelet transfusion prior to central line insertion versus platelet transfusion prior to central line insertion when:
- platelet count is less than 10×10^9/L or;
- platelet count is less than 20×10^9/L or;
- platelet count is less than 30×10^9/L or;
- platelet count is less than 50×10^9/L.

2) Platelet transfusion prior to central line insertion when platelet count is less than 50×10^9/L versus platelet transfusion prior to central line insertion when:
- platelet count is less than 10×10^9/L or;
- platelet count is less than 20×10^9/L or;
- platelet count is less than 30×10^9/L.

We will report each analysis separately, as subgroups within the main comparisons.

Types of outcome measures

Primary outcomes

- Major procedure-related bleeding within 24 hours of the procedure.

For example: a significant fall in haemoglobin (Hb) e.g. 20 g/L or greater in the absence of another cause; a fall in systolic blood pressure (SBP) by at least 20 mmHg or increase in heart rate by at least 20 beats per minute (BPM) or greater; haemothorax; requiring an intervention such as a transfusion required to treat bleeding; or major bleeding (not further defined) as reported by individual studies.
- All-cause mortality up to 30 days after the procedure.

Secondary outcomes

- Minor procedure-related bleeding within 24 hours of the procedure (defined as prolonged bleeding at the insertion site which only requires treatment with a pressure bandage, or haematoma at the insertion site), or minor bleeding (not further defined) as reported by individual studies.

- Serious adverse events.

- ○ Transfusion-related complications within 24 hours of the procedure (including transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions).
- ○ Line-related complications within seven days of the procedure (infection, thrombosis, other).
- Duration of hospital stay (total number of days in hospital).

- Proportion of patients receiving platelet transfusions and red cell transfusions within 24 hours of the procedure.

- Quality of life, as defined by the individual studies.

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) will formulate the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

We will limit our searches to five main electronic databases and two ongoing trial databases.
- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) (Appendix 1).
- MEDLINE (1946 to present) (Appendix 2).
- Embase (1974 to present) (Appendix 3).
- PubMed (e-publications only) (Appendix 4).
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to present) (Appendix 5).
- WHO International Clinical Trials Registry Platform (ICTRP) (Appendix 6).
- ClinicalTrials.gov (Appendix 6).

We will combine searches in MEDLINE with the Cochrane RCT search filter, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We will combine searches in Embase with the relevant Scottish Intercollegiate Guidelines Network (SIGN) RCT studies filter (www.sign.ac.uk/methodology/filters.html). We will exclude studies published in languages other than English. We will not limit searches by year of publication or publication type.

Searching other resources

We will handsearch reference lists of included studies in order to identify further relevant studies. We will make contact with lead authors of the included studies to identify any unpublished material, missing data or information regarding ongoing studies.

Data collection and analysis

Selection of studies

We will select studies according to chapter seven of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two review authors (MD, LE) will independently screen all the remaining references for relevance against the full eligibility criteria using DistillerSR software. We will retrieve full text articles for all references for which a decision on eligibility cannot be made from title and abstract alone. We will request additional information from study authors as necessary to assess the eligibility for inclusion of individual studies. The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, we will refer the decision of eligibility to a third review author (SS). We will report the results of study selection using a PRISMA flow diagram (Moher 2009).

Data extraction and management

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), two review authors (MD, LE) will independently extract data onto standardised forms using DistillerSR software. The data extraction form will be piloted on two included RCTs. The review authors will try to come to a consensus; if an agreement cannot be reached, they will consult a third review author (SS). The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. They will extract the following information for each study.

1. Source: Study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details.

2. General study information: Publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed.

3. Study details and methods: Location; country; setting; number of centres; total study duration; recruitment dates; length of follow-up; power calculation; primary analysis (and definition); stopping rules; method of sequence generation; allocation concealment; blinding (of clinicians, participants and outcome assessors); and any concerns regarding bias.

4. Characteristics of interventions: Number of study arms; description of experimental arm; description of control arm; type of platelet component (e.g. apheresis or pooled); dose of platelet component.

5. Characteristics of participants: Age; gender; primary diagnosis; type of catheter inserted; route and method of catheter insertion; platelet count.

6. Participant flow: Total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for review outcomes); number of allocated patients who received planned treatment; number of drop-outs with reasons (percentage in each arm); protocol violations; missing data.

7. Outcomes: Major procedure-related bleeding within 24 hours of the procedure; minor procedure-related bleeding within 24 hours of the procedure; transfusion-related complications within 24 hours of the procedure; line-related complications within seven days of the procedure; duration of hospital stay; proportion of patients receiving platelet and red cell transfusions within 24 hours of the procedure; all-cause mortality up to 30 days from the procedure; quality of life (as defined by the individual studies).

Assessment of risk of bias in included studies

We will perform an assessment of all RCTs using the Cochrane 'Risk of bias' tool according to chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (MD, LE) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear risk of bias'. We will report a brief description of the judgement statements upon which the authors have assessed potential bias in the 'Characteristics of Included Studies' table. We will ensure that a consensus on the degree of risk of bias is met through comparison of the review authors' statements and where necessary, through consultation with a third review author (SS). We will use the Cochrane Collaboration's tool for assessing risk of bias, that will include the following domains.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel.
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting.
- Other bias.

Measures of treatment effect

For continuous outcomes we will record the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we will present the standard mean difference (SMD). If available, we will extract and report hazard ratios (HRs) for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007).

For dichotomous outcomes we will report the pooled risk ratio (RR) with a 95% CI. Where the number of observed events is small (< 5% of sample per group), and where trials have balanced treatment groups, we will report the Peto's Odds Ratio (OR) with 95% CI (Deeks 2011).

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

Where appropriate, we will report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with CIs.

If we cannot report the available data in any of the formats described above, we will perform a narrative report, and if appropriate we will present the data in tables.

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster-randomised trials, cross-over studies, and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If patients are randomised more than once we will contact the authors of the study to provide us with data on the CVCs associated with the initial randomisation. For studies with multiple treatment groups MD and LE will exclude subgroups that are considered irrelevant to the analysis. We will tabulate all subgroups in the 'Characteristics of Included Studies' section. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011c).

Dealing with missing data

Where data are identified to be missing or unclear in published literature, we will contact study authors directly. We will record the number of patients lost to follow-up for each study. Where possible, we will analyse data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per protocol analyses (Higgins 2011c).

Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if $I^2 > 50\%$, or considerable if $I^2 > 80\%$. We perceive that we will identify at least moderate clinical and methodological heterogeneity within the studies selected for inclusion; in such cases, we will use the random-effects model. If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where we identify at least 10 studies for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Lau 2006; Sterne 2011).

Data synthesis

We will perform analyses according to the recommendations of chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into the Review Manager 5 software (RevMan 2014). One review author (LE) will enter the data and a second (MD) will then check for accuracy.

Where meta-analysis is feasible, we will use the random-effects model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and the inverse variance method (and standardised mean differences as necessary) for continuous outcomes. We will use the generic inverse variance method for time-to-event outcomes.

If heterogeneity is found to be above 80%, we will not perform a meta-analysis; rather we will comment on results as a narrative, and comment on any trends in the data within the results section of the review.

Summary of findings

We will use the GRADE approach to create a 'Summary of findings' table, as suggested in chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will use the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations.

1. Risk of Bias: serious or very serious
2. Inconsistency: serious or very serious
3. Indirectness: serious or very serious
4. Imprecision: serious or very serious

5. Publication bias: likely or very likely

We will report separate 'Summary of findings' tables for: prophylactic platelet transfusion versus no prophylactic platelet transfusion prior to the procedure; and a lower platelet count threshold versus the highest commonly used threshold (50×10^9/L). We will report the subgroup for each comparison that contains the largest number of studies.

The outcomes we will include are listed below.

1. Major procedure-related bleeding within 24 hours of the procedure.

2. All-cause mortality up to 30 days after the procedure.

3. Minor procedure-related bleeding within 24 hours of the procedure.

4. Respiratory deterioration attributable to transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), or transfusion-associated dyspnoea (TAD) within 24 hours of the procedure.

5. Line-related complications within seven days of the procedure (infection, thrombosis, other)

6. Proportion of patients receiving platelet transfusions within 24 hours of the procedure.

7. Quality of life.

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity.

• Type of central line inserted (venous tunnelled, venous untunnelled, portacath, whether an emergency or elective procedure).

• Type of patient (intensive care, liver disease, leukaemia, other).

• Age of patient (neonate, child (1 to 15 years), adult (16 years or older)).

• Whether patients had associated clotting abnormalities, including disseminated intravascular coagulation (DIC).

If appropriate, we will also investigate heterogeneity between studies as follows.

• Type of platelet component.

• Dose of platelet component.

Sensitivity analysis

We will assess the robustness of our findings by performing the following sensitivity analyses where appropriate.

• Including only those studies with a 'low risk of bias' (for example, RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).

• Including only those studies with less than a 20% drop-out rate.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Blood Platelets] explode all trees
#2 (platelet* or thrombocyte*):ti
#3 MeSH descriptor: [Platelet Transfusion] explode all trees
#4 MeSH descriptor: [Plateletpheresis] explode all trees
#5 ((platelet* or thrombocyte*) near/5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product or products or component* or concentrate* or apheres* or pooled or single donor* or random donor*))
#6 thrombocyt?pheres* or plateletpheres*

#7 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 MeSH descriptor: [Catheterization, Central Venous] this term only

#10 MeSH descriptor: [Catheters, Indwelling] this term only

#11 MeSH descriptor: [Central Venous Catheters] this term only

#12 MeSH descriptor: [Vascular Access Devices] this term only

#13 hickman* or "port catheter*" or port-a-cath* or "invasive line*" or portacath* or TIVAD*

#14 ((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or "in-dwelling" or implant* or placement* or subclavian or femoral or jugular) near/5 (catheter* or line* or cannul* or port*))

#15 ((vascular or venous) next (access* or reservoir*))

#16 #9 or #10 or #11 or #12 or #13 or #14 or #15

#17 #8 and #16

Appendix 2. MEDLINE search strategy

1. Catheterization, Central Venous/
2. Catheters, Indwelling/
3. Central Venous Catheters/
4. Vascular Access Devices/
5. (hickman* or port-a-cath* or port catheter* or port-a-cath* or invasive line* or portacath* or TIVAD*).tw.
6. ((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or "in-dwelling" or implant* or placement* or subclavian or femoral or jugular) adj5 (catheter* or line* or cannul* or port*)).tw.
7. ((vascular or venous) adj2 (access* or reservoir*)).tw.
8. or/1-7
9. Platelet Transfusion/
10. Plateletpheresis/
11. Blood Platelets/
12. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
13. (thrombocytopheres* or plateletpheres*).tw.
14. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
15. (platelet* or thrombocyte*).ti.
16. or/9-15
17. 8 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomi*.tw.
21. placebo.ab.
22. clinical trials as topic.sh.
23. randomly.ab.
24. groups.ab.
25. trial.tw.
26. or/18-25
27. exp animals/ not humans.sh.
28. 26 not 27
29. 17 and 28

Appendix 3. Embase search strategy

1. exp Central Venous Catheterization/
2. exp Indwelling Catheter/
3. exp Central Venous Catheter/
4. Vascular Access Devices/
5. (hickman* or port-a-cath* or port catheter* or port-a-cath* or invasive line* or portacath* or TIVAD*).tw.
6. ((central* or venous* or vascular* or intravenous* or tunnel* or indwelling or "in-dwelling" or implant* or placement* or subclavian or femoral or jugular) adj5 (catheter* or line* or cannul* or port*)).tw.
7. ((vascular or venous) adj2 (access* or reservoir*)).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Thrombocyte Transfusion/
10. Thrombocytopheresis/
11. Thrombocyte/
12. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
13. (thrombocyt?pheres* or plateletpheres*).tw.
14. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
15. (platelet* or thrombocyte*).ti.
16. or/9-15
17. 8 and 16
18. Randomized Controlled Trial/
19. Randomization/
20. Single Blind Procedure/
21. Double Blind Procedure/
22. Crossover Procedure/
23. Placebo/
24. exp Clinical Trial/
25. Prospective Study/
26. (randomi* or double-blind* or single-blind* or RCT*).tw.
27. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
28. (crossover* or cross over* or cross-over* or placebo*).tw.
29. ((treble or triple) adj blind*).tw.
30. or/18-29
31. Case Study/
32. case report*.tw.
33. (note or editorial).pt.
34. or/31-33
35. 30 not 34
36. (animal* or cat or cats or dog or dogs or pig or pigs or sheep or rabbit* or mouse or mice or rat or rats or feline or canine or porcine or ovine or murine or model*).ti.
37. 35 not 36
38. limit 37 to embase
39. 17 and 38

Appendix 4. PubMed search strategy (epublications only)

#1 hickman* OR port catheter* OR port-a-cath* OR "invasive line" OR portacath* OR TIVAD*
#2 ((central* OR venous* OR vascular* OR intravenous* OR tunnel* OR indwelling OR "in-dwelling" OR implant OR implants OR placement* OR subclavian OR femoral OR jugular) AND (catheter* OR line OR lines OR cannul* OR port OR ports))
#3 ((vascular OR venous) AND (access* OR reservoir*))
#4 #1 OR #2 OR #3
#5 ((platelet* OR thrombocyte*) AND (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR single donor* OR random donor*))
#6 (thrombocytopheres* OR plateletpheres*)
#7 ((platelet* OR thrombocyte*) AND (protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
#8 platelet*[TI] OR thrombocyte*[TI]
#9 #5 OR #6 OR #7 OR #8
#10 #4 AND #9
#11 (random* OR blind* OR control group OR placebo OR controlled trial OR controlled study OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#12 #10 AND #11

Appendix 5. Transfusion Evidence Library search strategy

TRANSFUSION EVIDENCE LIBRARY
Clinical Specialty: Haematology and Oncology AND Subject Area: Platelets
OR
(All fields: vascular OR venous OR invasive OR intravenous OR tunnel OR indwelling OR implant OR subclavian OR femoral OR jugular OR hickman OR catheter OR line OR access OR reservoir OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Keywords: platelets OR platelet transfusion)

Appendix 6. Ongoing Trial Register search strategies

WHO ICTRP
(Title: vascular OR venous OR invasive OR intravenous OR tunnel OR indwelling OR implant OR subclavian OR femoral OR jugular OR hickman OR catheter OR line OR access OR reservoir OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Intervention: platelets)
ClinicalTrials.gov
(Title: hickman OR catheter OR line OR access OR reservoir OR port-a-cath OR portacath OR cannula OR port OR ports) AND (Intervention: platelets OR platelet transfusion)

CONTRIBUTIONS OF AUTHORS

Michael Desborough: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis and content expert.

Lise Estcourt: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis

and content expert.

Simon Stanworth: protocol development and content expert.

Carolyn Doree: protocol development, searching and selection of studies.

Marialena Trivella: protocol development and statistical expert.

Sally Hopewell: protocol development and methodological expert.

DECLARATIONS OF INTEREST

Michael Desborough: none known.

Lise Estcourt: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Simon Stanworth: none known.

Carolyn Doree: none known.

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NOTES

This review will be a rapid review (definition of a rapid review as previously agreed with the Haematological Malignancies Group), we will only include English language publications.