Cochrane Library

Cochrane Database of Systematic Reviews

Prophylactic platelet transfusions prior to surgery for people with a low platelet count (Protocol)

Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J

Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J.
Prophylactic platelet transfusions prior to surgery for people with a low platelet count.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012779.
DOI: 10.1002/14651858.CD012779.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Prophylactic platelet transfusions prior to surgery for people with a low platelet count

Lise J Estcourt[1], Reem Malouf[2], Carolyn Doree[3], Marialena Trivella[4], Sally Hopewell[5], Janet Birchall[6]

[1]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK. [2]National Perinatal Epidemiology Unit (NPEU), University of Oxford, Oxford, UK. [3]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [4]Centre for Statistics in Medicine, University of Oxford, Oxford, UK. [5]Oxford Clinical Trials Research Unit, University of Oxford, Oxford, UK. [6]Haematology/Transfusion Medicine, NHS Blood and Transplant, Bristol and North Bristol NHS Trust, Bristol, UK

Contact address: Lise J Estcourt, Haematology/Transfusion Medicine, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headington, Oxford, OX3 9BQ, UK. lise.estcourt@nhsbt.nhs.uk, lise.estcourt@ndcls.ox.ac.uk.

Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 9, 2017.

Citation: Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J. Prophylactic platelet transfusions prior to surgery for people with a low platelet count. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012779. DOI: 10.1002/14651858.CD012779.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the clinical effectiveness and safety of prophylactic platelet transfusions prior to surgery for people with a low platelet count or platelet dysfunction (inherited or acquired).

BACKGROUND

Description of the condition

Platelets are an essential component in the formation of a blood clot (BCSH 2003). A low platelet count can lead to a range of bleeding symptoms such as bruising, nosebleeds and, rarely, life-threatening or fatal bleeding.

Thrombocytopenia is defined as a platelet count less than 150 x 10^9/L (BCSH 2003). When this is dilutional, associated with an expanded blood volume, the drop is mild and rarely clinically significant. Severe thrombocytopenia is defined as a platelet count less than 50 x 10^9/L (BCSH 2003). Thrombocytopenia can be caused by: reduced platelet production in the bone marrow often as a result of chemotherapy or a haematological malignancy (blood cancer) (Leguit 2010; Weinzierl 2013); increased platelet consumption as occurs in bleeding or disseminated intravascular coagulation (DIC) (Levi 2009); increased platelet destruction such as immune thrombocytopenia (Neunert 2013; Pacheco 2011; Provan 2010); or a combination of these conditions .

Mild, dilutional thrombocytopenia is common in pregnancy (7% to 12% of pregnancies), but severe thrombocytopenia (platelet count less than 50 x 10^9/L) is much less common (0.05% to 1% of pregnancies) and is a sign of complications (Burrows 1990; Nisha 2012; Sainio 2000). A platelet count less than 150 x 10^9/L is very common in individuals with chronic liver disease (up to 76%) (Afdhal 2008), and people who are critically ill (up to 68%) (Hui 2011). A large United Kingdom (UK) study of patients admitted to the intensive care unit (ICU) reported that 9% developed severe thrombocytopenia (Stanworth 2013). Thrombocy-

topenia is also frequent in people with haematological malignancies (Leguit 2010; Weinzierl 2013), and most platelet transfusions are used in individuals with haematological disorders (Cameron 2007; Greeno 2007; Pendry 2011).

People with thrombocytopenia often require a surgical procedure. A low platelet count is a relative contraindication to surgery due to the risk of bleeding (Estcourt 2017; Kaufman 2015; NICE 2015). Platelet transfusions are one of a number of interventions used in modern clinical practice to prevent and treat bleeding in people with thrombocytopenia.

Description of the intervention

Platelet concentrates are the second most frequently used blood component (Bolton-Maggs 2016). Approximately 2.2 million platelet units are transfused annually in the USA (Whitaker 2013). Seventy-four per cent of platelet transfusions are given prophylactically to non-bleeding thrombocytopenic people and 15% are given to prevent bleeding prior to surgery or a procedure in people with haematological malignancies. In many cases platelet transfusions are given at platelet counts higher than the recommended triggers (Estcourt 2012; Greeno 2007).

Unlike other blood components, platelets must be kept on a shaker at room temperature, limiting the shelf life of platelet units to five to seven days. This makes it difficult for hospitals to manage their platelet stock (Fuller 2011).

Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to surgery. Guidelines often recommend a platelet count threshold of 50 x 10^9/L prior to major surgery and 100 x 10^9/L prior to surgery involving the brain or eyes (Estcourt 2017; Kaufman 2015; NICE 2015). Guidelines often do not go into further detail about risks for different types of surgery. Some low-risk surgery may not require platelet transfusions at all, other procedures may be higher risk and the risk may also be dependent on patient co-morbidities.

Platelet transfusions are not risk-free. In 2014, 34% of all transfusion-related adverse events reported to the UK national reporting system (Serious Hazards of Transfusion (SHOT)) were due to platelet components. The most common adverse events due to platelet components were febrile and allergic reactions (Birchall 2015). Although most of these reactions are not life-threatening they can be extremely distressing for the person and time consuming for health professionals to investigate and exclude a more serious cause. Rarer, but more serious sequelae, include: anaphylaxis (life-threatening allergic reaction), transfusion-transmitted infections (TTI) and transfusion-related acute lung injury (TRALI) (Blumberg 2010; Chapman 2015; Kaufman 2015; Slichter 2007; Vlaar 2013). Platelets units are stored at room temperature on a shaker, which increases the risk of bacterial growth (1:2000 to 1: 3000) (Jacobs 2011). In 2015, there were four near miss incidents (three in platelets) reported to the unit between 2011 and 2015 and a total of 37/44 bacterial transfusion-transmissions to individual recipients (34 incidents) were caused by the transfusion of platelets (Serious Hazards of Transfusion (SHOT) 2015).

A recent prospective multicentre cohort study concluded that in critically ill people, transfusion of platelets, but not of red blood cells and plasma, is an independent risk factor for acquiring a nosocomial infection (Engele 2016).

Alternative agents which could replace or reduce platelet transfusions may be more effective than platelet transfusions at controlling bleeding and will have a different side-effect profile. Alternatives include artificial platelet substitutes, cryosupernatant, recombinant factor VIIa (rFVIIa), fibrinogen, recombinant factor XIII (rFXIII), thrombopoietin (TPO) mimetics and antifibrinolytic drugs.

How the intervention might work

Platelet transfusions

The premise for pre-procedure intervention with platelet transfusion is as follows: thrombocytopenia increases the risk of bleeding, platelet transfusion corrects thrombocytopenia, a higher platelet count prevents bleeding and overall there is benefit to the patient. This presumption is however over simplistic.

In a small randomised controlled trial (RCT) of only 23 participants with thrombocytopenia who required 35 procedures and 84 teeth removed, bleeding complications were minimal without blood product support (Perdigão 2012).

One study including a total of 1720 patients with thrombocytopenia undergoing coronary artery bypass graft (CABG) surgery study pooled individual patient data from one pilot study and six RCTs. Platelet transfusion compared with no platelet transfusion was associated with a significant increase in mortality among patients undergoing CABG surgery (odds ratio (OR), 4.76; 95% confidence interval (CI), 1.65 to 13.73; P = 0.009). Although the authors used propensity score analysis, it is not clear if the increased mortality was due to platelet transfusion or because people who were more unwell received platelet transfusions (Spiess 2004).

Alternatives to platelet transfusions

Alternatives to platelet transfusion either simulate the effects of platelets (artificial platelet substitutes), stimulate additional fibrin formation (cryosupernatant, rFVIIa and fibrinogen), promote von Willebrand factor release and platelet function (desmopressin), increase platelet production (TPO mimetics), strengthen clot structure (rFXIII) or decrease clot breakdown (antifibrinolytics). These agents aim to promote haemostasis without the side effects associated with platelet transfusions. Their main adverse effect is excessive clotting and thrombosis.

In this review we will exclude trials that assess the use of: rFVIIa; fibrinogen concentrate; rFXIII; prothrombin complex concen-

trate; and desmopressin as these are the subject of other Cochrane reviews that compared these interventions to an active comparator in people requiring a surgical procedure (Desborough 2017; Fabes 2013; Simpson 2012).

Artificial platelet substitutes

Artificial platelet substitutes such as microspheres of human albumin coated with fibrinogen, lyophilised platelets, infusible plasma membranes, and liposomes with inserted platelet receptors aim to reproduce the active components of platelets without associated adverse events (Desborough 2016). Artificial platelets are not yet in routine clinical use, so their costs and adverse events are at present unclear.

Cryosupernatant

Cryosupernatant is a source of clotting factors and can be administered intravenously. It is a blood component and is associated with a small risk of transfusion reactions and transfusion-transmitted infections.

Thrombopoietin (TPO) mimetics

Thrombopoietin (TPO) is made by the liver and is the key regulator of bone marrow platelet production. TPO mimetics have been used in several disease states to promote both an increase in the cells that produce platelets (megakaryopoiesis) and the production of platelets themselves (thrombopoiesis) (Kuter 2014). The two main TPO mimetics in current use are romiplostim (weekly injection) and eltrombopag (daily oral tablet), both of which are recommended by the National Institute for Health and Care Excellence (NICE) for use in adults with immune thrombocytopenia (ITP) who have severe disease and a high risk of bleeding (NICE 2011; NICE 2013). While a systematic review found that these agents improve platelet counts, there was no evidence that they reduced the risk of significant bleeding for people with ITP (Zeng 2011). TPO mimetics are more expensive than platelet transfusions (Joint Formulary Committee 2016). Interleukin 6 and interleukin 11 may also act as stimulants of thrombopoiesis (Gordon 1995; Kurzrock 2011; Tsimberidou 2005). They are not in routine clinical use, so their costs are unclear at present.

Antifibrinolytic drugs

Fibrinolysis is the process by which blood clots are broken down after they have been formed. Anti-fibrinolytic drugs block this process, resulting in greater clot strength. The three most commonly used antifibrinolytic drugs are tranexamic acid, aprotinin and epsilon-aminocaproic acid. Other Cochrane systematic reviews have assessed these agents in people undergoing surgical procedures (Henry 2011; McNicol 2016), or in people with haematological disorders (Estcourt 2016a).

Why it is important to do this review

People with a low platelet count often require surgery. Current guidelines are mainly based on expert opinion rather than good evidence and frequently do not go into detail about the risks for different types of surgery or define a specific platelet count threshold. Some low- risk surgery, for example dental extraction may not require platelet transfusions at all. Platelet transfusions may cause immediate- or longer- term harm and delay the start of life-saving treatments. Alternatives to platelets may be more effective and safer. There is therefore a need to assess the likely benefit of platelet transfusion and their alternatives, in different procedures, against known risks.

In this review we aim to answer the following questions.

Do people require prophylactic platelet transfusion prior to certain types of surgery?

If platelet transfusions are required, which platelet count threshold should be used to trigger the transfusion of prophylactic platelets prior to surgery?

Are prophylactic platelet transfusions superior to other alternative treatments?

OBJECTIVES

To determine the clinical effectiveness and safety of prophylactic platelet transfusions prior to surgery for people with a low platelet count or platelet dysfunction (inherited or acquired).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs) and controlled before-after studies (CBAs), irrespective of language or publication status. We will exclude uncontrolled studies, cross-sectional studies and case-control studies.

We will only include cluster-RCTs, non-randomised cluster trials, and CBAs with at least two intervention sites and two control sites. In studies with only one intervention or control site, the intervention (or comparison) is completely confounded by the study site, making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables.

If there are sufficient data to answer this review's questions using only data from RCTs, we will only report data from RCTs.

Types of participants

People of all ages with a low platelet count who are due to have surgery.

We will exclude studies on people with a low platelet count who are actively bleeding because they will receive platelet transfusions as part of the treatment of bleeding.

Types of interventions

We will include RCTs, non-RCTs and controlled before-after studies (CBAs) comparing three types of platelet transfusion regimens.

Comparison 1:. Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery (placebo or no treatment).

Comparison 2: Prophylactic platelet transfusion prior to surgery versus alternative treatments (cryosupernatant, antifibrinolytics, thrombopoietin (TPO) mimetics). In this review we will exclude trials that assess the use of recombinant factor VIIa (rFVIIa); fibrinogen concentrate, recombinant factor XIII (rFXIII), prothrombin complex concentrate, and desmopressin as these are the subject of other Cochrane reviews that compared these interventions to an active comparator in people requiring a surgical procedure (Desborough 2017; Fabes 2013; Simpson 2012).

Comparison 3: Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery.

We will record type of platelet component and dose of platelet component received.

Types of outcome measures

Primary outcomes

- Mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery.
- The number of participants with major procedure-related bleeding within seven days of surgery, defined as:
    - surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing;
    - bleeding of sufficient size to cause delayed wound healing, or wound infection or surgical site bleeding that is unexpected and prolonged or causes haemodynamic instability (as defined by the study) that is associated with a 20 g/L drop in haemoglobin (Hb);
    - bleeding that requires two or more units of whole blood/red cells within 24 hours of the bleeding;
    - bleeding defined by the study with no further details.

Secondary outcomes

- The number of participants with minor procedure-related bleeding within seven days of surgery (e.g. haematoma, prolonged bleeding at surgical site that does not fulfil the definition for major bleeding).
- Number of platelet transfusions per participant and number of platelet components per participant.
- Number of red cell transfusions per participant and number of red cell components per participant.
- Proportion of participants requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen) within seven days from the surgery.
- Quality of life assessment using validated tools.
- Serious adverse events due to:
    - transfusion (transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion related infection, transfusion-associated circulatory overload (TACO), transfusion-related dyspnoea) within 24 hours of the transfusion;
    - surgery (e.g. delayed wound healing, infection) within 30 days after the operation.
- Length of hospital stay and length of intensive therapy unit (ITU) stay.
- Venous and arterial thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction).

Search methods for identification of studies

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

Electronic searches

We will search the following databases.

Bibliographic databases

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue) (Appendix 1)
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process and other Non-Indexed Citations, and 1946 to present) (Appendix 2)
- PubMed (for e-publications ahead or print only) (www.ncbi.nlm.nih.gov/pubmed) (Appendix 3)
- Embase (OvidSP, 1974 to present) (Appendix 4)
- CINAHL (EBSCOHost, 1937 to present) (Appendix 5)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to present - this includes a search of grey literature) (Appendix 6)
- LILACS (1982 to present) (http://lilacs.bvsalud.org/en/) (Appendix 7)

- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present) (Appendix 8)

Online databases of on-going trials

- ClinicalTrials.gov (clinicaltrials.gov) (Appendix 9)
- WHO International Clinical Trials Registry Search Platform (ICTRP) (apps.who.int/trialsearch/AdvSearch.aspx) (Appendix 10).

We will combine searches in MEDLINE and Embase with the recommended Cochrane RCT search filters (Lefebvre 2011), systematic review filters based on those of the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html) and controlled before-after studies filters based on those used in reviews of the Cochrane Effective Practice and Organisation of Care Group (EPOC 2015) (http://epoc.cochrane.org/). Searches in CINAHL will be combined with the SIGN systematic review and RCT filter and an EPOC-based filter. We will not limit searches by language, year of publication or publication type.

Once we identify studies for inclusion we will search MEDLINE (OvidSP) for errata or retraction statements for the reports of these studies.

Searching other resources

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

Data collection and analysis

We will summarise data in accordance with standard Cochrane methodologies. We will analyse data from different study designs separately.

Selection of studies

We will select studies with reference to the methods outlined in 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 (LE, RM) will independently screen all the remaining references for relevance against the full eligibility criteria. Full-text papers will be retrieved for all references for which a decision on eligibility cannot be made from only screening title and abstract. If necessary additional information will be requested from study authors 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 when it is not possible, the decision of eligibility will be referred to a third review author (MT). The results of study selection will be reported using a PRISMA flow diagram (Moher 2009). We will record the reasons for excluding studies based on full-text assessment and will add those to the 'Characteristics of excluded studies' table.

Multiple reports of one study will be collated so that the study, and not the report, is the unit of analysis.

Data extraction and management

Two review authors (RM, LE) will independently extract data as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), using standardised forms available in Covidence software (Covidence 2016). Two different data extraction forms will be piloted for included RCTs and NRS separately. If an agreement cannot be reached, the two review authors will try to come to a consensus; they will seek the advice of a third review author (MT). 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.

For randomised controlled trials

- Source: study ID, report ID, review author ID, date of extraction, ID of author checking extracted data, citation of paper, contact author's details.
- General study information: publication type, study objectives, funding source, conflict of interest declared, other relevant study publication reviewed.
- Study details and methods: location, country, clinical setting, number of centres, study design, 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.
- 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, thresholds of platelets transfusions, type of surgery.
- Characteristics of participants: age, gender, primary diagnosis, surgery types procedure (minor, major, surgery to sensitive areas as ocular surgery or neurosurgery), platelet count, coagulation abnormalities, anticoagulant medications, antiplatelet medications.
- 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 participants who received planned treatment, number of dropouts with reasons (percentage in each arm), protocol violations, missing data.
- Method of data analyses.

- Outcomes: mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery; number of participants with major procedure-related bleeding within seven days of surgery; number of participants with minor procedure-related bleeding within seven days of surgery; number of platelet transfusions per participant and number of platelet components per participant; number of red cell transfusions per participant and number of red cell components per participant; proportion of participants requiring additional interventions to stop bleeding within seven days from the surgery; quality of life assessment using validated tools; serious adverse events due to transfusion (within 24 hours of the transfusion) or surgery (within 30 days after the operation); length of hospital stay and length of ITU stay, venous and arterial thromboembolism..

For Non-randomised controlled trials

In addition to all the information listed for RCTs we will extract information on the following.

- Study design.
- Method of selecting participants: sample source, sample size, participants eligibility criteria, number of participants at each follow-up point. and the source of study control group and baseline differences between the two groups.
- Confounding factors: baseline confounding factors and co-interventions that might lead potentially to bias are identified in the study and relevant confounding factors and co-interventions that could introduce bias after the starting of platelets transfusions; the comparability of groups on confounding factors.
- Method of assigning the intervention.
- Co-intervention status: this is in order to document if any other co-interventions are considered in the study.
- Method of data analysis: methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in chapter 13 of the*Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

Assessment of risk of bias in included studies

Randomised controlled trials (RCTs)

We will assess the risk of bias for all included 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 (LE, RM) 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 review 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 (SH). We will use Cochrane's tool for assessing risk of bias, that will include the following domains.

- Selection bias: we will describe for each included study if and how the allocation sequence was generated and if allocation was adequately concealed prior to assignment. We will also describe the method used to conceal the allocation sequence in detail and determine if intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
- Performance bias: we will describe for each included study, where possible, if the study participants and personnel were adequately blinded from knowledge of which intervention a participant received. We will judge studies as low risk of bias if they were blinded, or if we judge that lack of blinding could not have affected the results.
- Detection bias: was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?
- Incomplete outcome data: we will describe for each included study the attrition bias due to amount, nature or handling of incomplete outcome data. We will also try to evaluate whether intention-to-treat analysis has been performed or could be performed from published information.
- Selective outcome reporting or reporting bias: we will describe for each included study the possibility of selective outcome reporting bias.
- Other bias: was the study apparently free of other problems that could put it at risk of bias?

We will summarise the risk of bias for each key outcome for each included study. We will judge studies with at least one domain of high risk at high risk of bias overall etc.

Non-randomised controlled trials (non-RCTs)

We will use ROBINS-I tool (formerly known as ACROBAT-NRSI) to rate the quality of non-randomised controlled trials (non-RCTs) and controlled before-after studies (CBAs) studies (Sterne 2016). This tool is based on the Cochrane 'Risk of bias' tool for rating the quality of RCTs (Higgins 2011c). The tool covers seven domains and the quality of evidence is rated 'low', 'moderate', 'serious', 'critical or no information', and the response options are 'yes', 'probably yes', 'no', 'probably no' and 'no information', (see Appendix 11 for a copy of the tool) and uses signalling questions for the assessment of:

- bias due to confounding;
- bias in the selection of participants;
- bias in measurement of interventions;
- bias due to departure from intended interventions;
- bias due to missing data;
- bias in measurement of outcomes;

- bias in the selection of the reported result.

For 'low risk of bias' the study is judged to be at low risk of bias on all of the tool's seven domains.
For 'moderate risk of bias' the study is judged to be at low to moderate risk of bias in all of the tool's seven domains.
For 'serious risk of bias ' the study is judged to be at serious risk of bias in at least one of the tool's seven domains.
For "critical risk of bias' to study is judged to be at critical risk of bias in at lease one domain of the tool's seven domains.
For 'no information on bias' when information in one or more key 'Risk of bias' domains are lacking.
Two review authors (LE, RM) will assess independently each domain of potential bias listed and will also tabulate 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 (SH). We will highlight the highest quality evidence for each outcome.
We have pre-specified the following main potential confounding factors.

- Primary diagnosis of patient (e.g. liver disease; critical illness; pregnancy)
- Age: variability in the age of patients included, e.g. paediatric (less than 16 years) versus adult (> 16 years) versus older adult (> 60 years)
- Gender: male to female ratio
- Previous severe bleeding (e.g. World Health Organization (WHO) grade 3 or 4 or equivalent)

Measures of treatment effect

Randomised controlled trials (RCTs)

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). If continuous outcomes are reported using different scales, we will use standardised mean difference (SMD).
If available, we will extract and report hazard ratios (HRs) for time-to-event-data (mortality or time in hospital) 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). If sufficient studies provide HRs, we will use HRs in favour of risk ratios (RRs) or MDs in a meta-analysis, but for completeness, we will also perform a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.
For dichotomous outcomes, we will report the pooled RR with a 95% CI. (Deeks 2011). 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).
For cluster-RCTs, we will extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice (MT) to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).
If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

Non-randomised studies (Non-RCTs)

For dichotomous outcomes, if available we will extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of risk ratios (i.e. the risk ratio post-intervention/risk ratio pre-intervention). For continuous variables, if available we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group) (EPOC 2015).
If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

All studies

Where appropriate, we will report the number needed to treat to for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with 95% 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-RCTs, 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 participants are randomised more than once, we will contact the authors of the study to provide us with data associated with the initial randomisation. For studies with multiple treatment groups, two review authors (RM and LE) will exclude subgroups that are considered irrelevant to the analysis. We will tabulate all subgroups in the 'Characteristics of included studies' table. 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 we identify data to be missing or unclear in published literature, we will contact study authors directly. If unsuccessful, our analysis will be based on the number reaching follow-up and we will perform analysis for worse- and best-case scenarios. We will record the number of patients lost to follow-up for each study. Where possible, we will analyse data by intention-to-treat (ITT), but if insufficient data are available, we will present per protocol (PP) analyses (Higgins 2011c).

Assessment of heterogeneity

We will analyse the data in RCTs, non-RCTs, and CBA studies separately.

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data and perform a meta-analysis. We will assess the extent of heterogeneity by both visual inspection of forest plots and utilising statistical methods.

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 low if $I^2 \leq 50\%$, moderate if I^2 is 50% to 80% or considerable if I^2 is > 80%. We will use the random-effects model for low to moderate heterogeneity. If statistical heterogeneity is considerable, the overall summary statistic will not be reported.

Potential causes of heterogeneity will be assessed by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

We will explore potential publication bias (small-trial bias) by generating a funnel plot and using a linear regression test if we find at least 10 studies are identified for inclusion in a meta-analysis, We will consider a P value < 0.1 as significant for this test (Sterne 2011). Data synthesis If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of Cochrane (Deeks 2011).

Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of Cochrane (Deeks 2011). We will not conduct meta-analyses that include both RCTs and non-RCTs. We will conduct separate meta-analyses for each comparison. Different thresholds within the comparisons will only be grouped together if they are considered to be clinically similar.

Randomised controlled trials (RCTs)

For RCTs where meta-analysis is feasible, we will use the random-effects model for pooling the data. For binary outcomes, we will base the estimation of the between-study variance on the Mantel-Haenszel estimator. We will use the inverse-variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. If heterogeneity is found to be above 80%, and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity then we will not perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

Non-randomised studies (non-RCTs)

If meta-analysis is feasible for non-RCTs or CBA studies, we will analyse non-RCTs and CBA studies separately. We will only analyse outcomes with adjusted effect estimates if these are adjusted for the same factors using the inverse-variance method as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

All studies

We will use the random-effects model for all analyses as we anticipate that true effects will be related but will not be the same for included studies. If we cannot perform a meta-analysis. we will comment on the results as a narrative with the results from all studies presented in tables.

'Summary of findings' table

We will use the GRADE tool (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of evidence for each outcome. We will present 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.

- Risk of Bias: serious or very serious

- Inconsistency: serious or very serious
- Indirectness: serious or very serious
- Imprecision: serious or very serious
- Publication bias: likely or very likely

The outcomes we will include are listed below in order of most relevant endpoints for participants.

- All-cause mortality
- Mortality secondary to bleeding
- Mortality secondary to thromboembolism
- Mortality secondary to infection
- Number of participants with major procedure-related bleeding within seven days of surgery
- Number of participants with minor procedure-related bleeding within seven days of surgery
- Serious adverse events due to platelet transfusions

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.

- Age of participant (neonate, infant, child, adult)
- Type of surgery: minor or major (cardiac, eye, neurosurgery, dental, orthopaedic, liver, obstetric, gynaecological, plastic, gastrointestinal)
- Underlying cause of thrombocytopenia (bone marrow failure due to disease or treatment, increased destruction of platelets, or increased consumption of platelets)
- Dose of platelet component
- Co-existing coagulopathy
- Co-existing platelet dysfunction (inherited or acquired)

Sensitivity analysis

We will assess the robustness of the results by performing the following sensitivity analyses when possible.

- Including studies with a 'low risk of bias' (e.g.RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).
- Including studies with less than a 20% dropout.

ACKNOWLEDGEMENTS

We thank the editorial base of the Cochrane Haematological Malignancies Review Group.

We thank the peer and consumer reviewers Dr. Julia Bohlius and Dr. Olaf Weingart of this protocol.

We thank NHS Blood and Transplant.

We thank the National Institute of Health Research (NIHR). This review is part of a series of reviews that have been funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. This research was also supported by the NIHR Oxford Biomedical Research Centre Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

REFERENCES

Additional references

Afdhal 2008
Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, et al. Thrombocytopenia associated with chronic liver disease. *Journal of Hepatology* 2008;**48**(6):1000–7.

BCSH 2003
BCSH. British Committee for Standards in Haematology: guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003;**122**(1):10–23.

Birchall 2015
Birchall J, Tinegate H, Regan F. Chapter 14 Acute transfusion reactions (ATR). In: Bolton-Maggs PHB, Poles D, et al.on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group, editor(s). *The 2014 Annual SHOT Report*. Manchester, UK: SHOT, 2015:106-12.

Blumberg 2010
Blumberg N, Heal JM, Phillips GL. Platelet transfusions: trigger, dose, benefits and risks. *F1000 Medicine Reports* 2010;**2**:1–5.

Bolton-Maggs 2016
Bolton-Maggs PHB, (Ed) Poles D, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2015 Annual SHOT Report. SHOT 2016.

Burrows 1990
Burrows RF, Kelton JG. Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *American Journal of Obstetrics and Gynecology* 1990;**162**:731–4.

Cameron 2007
Cameron B, Rock G, Olberg B, Neurath D. Evaluation of platelet transfusion triggers in a tertiary-care hospital. *Transfusion* 2007;**47**(2):206–11.

Chapman 2015
Chapman C. Transfusion-related lung injury (TRALI), 2015. www.shotuk.org/wp-content/uploads/SHOT-2014-Annual-Report_v11-Web-Edition.pdf (accessed 26 November 2015).

Covidence 2016 [Computer program]
Veritas Health Innovation. Covidence systematic review software. Melbourne: Veritas Health Innovation, 2016.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: HigginsJPT, Green S (editors). Cochrane Handbook for SystematicReviews of Interventions Version 5.1.0 (updated March2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Desborough 2016
Desborough MJR, Smethurst PA, Estcourt LJ, Stanworth SJ. Alternatives to allogeneic platelet transfusion. *British Journal of Haematology* 2016;**175**:381-92.

Desborough 2017
Desborough MJ, Oakland K, Brierley C, Bennett S, Doree C, Trivella M, et al. Desmopressin use for minimising perioperative blood transfusion. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD001884.pub3]

Engele 2016
Engele LJ, Straat M, van Rooijen IHM, de Vooght KMK, Cremer OL, Schultz M, et al. Transfusion of platelets, but not of red blood cells, is independently associated with nosocomial infections in the critically ill. *Annals of Intensive Care* 2016;**6**:67. [DOI: 10.1186/s13613-016-0173-1.]

EPOC 2015
Effective Practice, Organisation of Care (EPOC). EPOC Resources for review authors. Oslo: Norwegian KnowledgeCentre for the Health Services 2015. Available at: http://epoc.cochrane.org/epoc-specific-resources-review-authors.

Estcourt 2012
Estcourt LJ, Birchall J, Lowe D, Grant-Casey J, Rowley M, Murphy MF. Platelet transfusions in haematology patients: are we using them appropriately?. *Vox Sanguinis* 2012;**103**(4):284–93.

Estcourt 2016a
Estcourt LJ, Desborough M, Brunskill SJ, Doree C, Hopewell S, Murphy MF, et al. Antifibrinolytics (lysine analogues) for the prevention of bleeding in people with haematological disorders. *Cochrane Database of Systematic Reviews* 2016, Issue 3. [DOI: 10.1002/14651858.CD009733.pub3]

Estcourt 2017
Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. and the British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. *British Journal of Haematology* 2017;**176**:365–94. [DOI: 10.1111/bjh.14423]

Fabes 2013
Fabes J, Barker G, Simons G, Curry N, Brunskill SJ, Doree C, et al. Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD010649]

Fuller 2011
Fuller AK, Uglik KM, Braine HG, King KE. A comprehensive program to minimize platelet outdating. *Transfusion* 2011;**51**:1469-76. [DOI: 10.1111/j.1537-2995.2010.03039.x]

Gordon 1995
Gordon MS, Nemunaitis J, Hoffman R, Paquette RL, Rosenfeld C, Manfreda S, et al. A phase I trial of recombinant human interleukin-6 in patients with myelodysplastic syndromes and thrombocytopenia. *Blood* 1995;**85**:3066–76.

Greeno 2007
Greeno E, McCullough J, Weisdorf D. Platelet utilization and the transfusion trigger: a prospective analysis. *Transfusion* 2007;**47**:201-5. [DOI: 10.1111/j.1537-2995.2007.01089.x]

Henry 2011
Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD001886.pub4]

Higgins 2011a
Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c
Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in Statistics. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hui 2011
Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest* 2011;**139**(2):271–8.

Jacobs 2011
Jacobs MR, Smith D, Heaton WA, Zantek ND, Good CE. Detection of bacterial contamination in prestorage culture-negative apheresis platelets on day of issue with the Pan Genera Detection test. *Transfusion* 2011;**51**(12):2573-82.

Joint Formulary Committee 2016
Joint Formulary Committee. Joint Formulary Committee. *British National Formulary*. Online. London: BMJ Group and Pharmaceutical Press, 2016. Available at: https://www.medicinescomplete.com/mc/bnf/current. Accessed 17th March 2016.

Kaufman 2015
Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Annals of Internal Medicine* 2015;**162**(3):205-13.

Kurzrock 2011
Kurzrock R, Cortes J, Thomas DA, Jeha S, Pilat S, Talpaz M. Pilot study of low-dose interleukin-11 in patients with bone marrow failure. *Journal of Clinical Oncology* 2011;**19**(21):4165–72.

Kuter 2014
Kuter DJ. Milestones in understanding platelet production: a historical overview. *British Journal of Haematology* 2014;**165**(2):248–58.

Leguit 2010
Leguit RJ, van den Tweel JG. The pathology of bone marrow failure. *Histopathology* 2010;**57**(5):655–70.

Levi 2009
Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Journal of Haematology* 2009;**145**(1):24–33.

McNicol 2016
McNicol ED, Tzortzopoulou A, Schumann R, Carr DB, Kalra A. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database of Systematic Reviews* 2016, Issue 9. [DOI: 10.1002/14651858.CD006883.pub3]

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-Analyses: the PRISMA Statement. *Annals of Internal Medicine* 2009;**151**(4):264-9.

Neunert 2013
Neunert CE. Current management of immune thrombocytopenia. *Hematology* 2013;**2013**:276–82.

NICE 2011
NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. National Institute of Health and Care Excellence 2011:TA221.

NICE 2013
NICE. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). National Institute of Health and Care Excellence 2013:TA293.

NICE 2015
National Institute for Health and Clinical Excellence. Blood transfusion. https://www.nice.org.uk/guidance/ng24 Accessed 10 November 2016.

Nisha 2012
Nisha S, Amita D, Uma S, Tripathi AK, Pushplata S. Prevalence and characterization of thrombocytopenia in pregnancy in Indian women. *Indian Journal of Hematology and Blood Transfusion* 2012;**28**(2):77–81.

Pacheco 2011
Pacheco LD, Berkowitz RL, Moise KJ, Bussel JB, McFarland JG, Saade GR. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. *Obstetrics and Gynecology* 2011;**118**(5):1157–63.

Parmar 1998
Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34.

Pendry 2011
Pendry K, Davies T. An audit of use and wastage in the north west of England and North Wales: where have all the platelets gone?. *Blood and Transplant Matters* 2011;**34**:17–9.

Perdigão 2012
Perdigão JPV, de Almeida PC, Rocha TDS, Mota MRL, Soares ECS, Alves APNN, et al. Postoperative bleeding after dental extraction in liver pretransplant patients. *Journal of Oral and Maxillofacial Surgery* 2012;**70**:e177–84.

Provan 2010
Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;**115**(2):168–86.

Reeves 2011
Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomised studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

RevMan 2014 [Computer program]
Revman. The Nordic Cochrane Centre. The Cochrane Collaboration . Review Manager (RevMan). 5.3. The Nordic Cochrane Centre,. The Cochrane Collaboration; Copenhagen, 2014.

Sainio 2000
Sainio S, Kekomäki R, Riikonen S, Teramo K. Maternal thrombocytopenia at term: a population-based study. *Acta Obstetricia et Gynecologica Scandinavica* 2000;**79**:744–9.

Schünemann 2011a
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT,Green S (editors), Cochrane Handbook for SystematicReviews of InterventionsVersion 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Availablefrom handbook.cochrane.org.

Schünemann 2011b
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, DeeksJJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews

of InterventionsVersion 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Simpson 2012
Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD005011.pub4]

Slichter 2007
Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology* 2007;**1520**:172–8.

Spiess 2004
Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. *Transfusion* 2004;**44**(8):1143–8.

Stanworth 2013
Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll DLA. Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. *Transfusion* 2013;**53**(5):1050–8.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration. 2011. Available from handbook cochrane.org.

Sterne 2016
Sterne JAC, Hernán MA, Reeves C, Savovi
ć J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Tsimberidou 2005
Tsimberidou AM, Giles FJ, Khouri I, Bueso-Ramos C, Pilat S, Thomas DA, et al. Low-dose interleukin-11 in patients with bone marrow failure: update of the M. D. Anderson Cancer Center experience. *Annals of Oncology* 2005;**16**(1):139-45.

Vlaar 2013
Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. *Lancet* 2013;**382**(9896):984–94.

Weinzierl 2013
Weinzierl EP, Arber DA. The differential diagnosis and bone marrow evaluation of new-onset pancytopenia. *American Journal of Clinical Pathology* 2013;**139**(1):9–29.

Whitaker 2013
Whitaker BI. National Blood Collection and Utilization Survey Report. Washington, DC: U.S. Department of Health and Human Services; 2013. www.hhs.gov/ash/bloodsafety/2011-nbcus.pdf Accessed 01 December 2016.

Zeng 2011
Zeng Y, Duan X, Xu J, Ni X. TPO receptor agonist for chronic idiopathic thrombocytopenic purpura. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD008235.pub2]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library)

#1 MeSH descriptor: [Blood Platelets] explode all trees
#2 transfus*
#3 #1 and #2
#4 MeSH descriptor: [Platelet Transfusion] explode all trees
#5 MeSH descriptor: [Plateletpheresis] explode all trees
#6 ((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*))
#7 thrombo?ytopheres* or plateletpheres*
#8 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#9 #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Specialties, Surgical] explode all trees

#11 MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#12 MeSH descriptor: [Perioperative Care] explode all trees
#13 MeSH descriptor: [Perioperative Period] explode all trees
#14 surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

Appendix 2. MEDLINE (OvidSP)

1. Platelet Transfusion/
2. Plateletpheresis/
3. Blood Platelets/ and transfus*.mp.
4. ((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,kf.
5. (thromboc?topheres* or plateletpheres*).tw,kf.
6. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Perioperative Care/
9. exp Surgical Procedures, Operative/
10. exp Perioperative Period/
11. exp Specialties, Surgical/
12. (preoperat* or postoperat* or perioperat* or operat* or surg* or presurg* or postsurg* or perisurg* or transplant* or bypass* or arthroplasty or neurosurg*).mp.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. Meta-Analysis.pt.
16. ((meta analy* or metaanaly*) and (trials or studies)).ab.
17. (meta analy* or metaanaly* or evidence-based).ti.
18. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.
19. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
20. Cochrane Database of systematic reviews.jn.
21. (additional adj (papers or articles or sources)).ab.
22. ((electronic* or online) adj (sources or resources or databases)).ab.
23. (relevant adj (journals or articles)).ab.
24. or/15-23
25. Review.pt.
26. RANDOMIZED CONTROLLED TRIALS AS TOPIC/
27. selection criteria.ab. or critical appraisal.ti.
28. (data adj (abstraction or extraction or analys*)).ab.
29. RANDOMIZED CONTROLLED TRIAL/
30. or/26-29
31. 25 and 30
32. 24 or 31
33. exp CONTROLLED CLINICAL TRIAL/
34. exp CONTROLLED CLINICAL TRIALS AS TOPIC/
35. (randomi* or trial).tw,kf.
36. (placebo or randomly or groups).ab.
37. or/33-36
38. CONTROLLED BEFORE-AFTER STUDIES/

39. INTERRUPTED TIME SERIES ANALYSIS/
40. (nonrandom* or non random*).tw,kf.
41. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.
42. (controlled clinical study or controlled study or control group*).tw,kf.
43. ((before adj3 after) or "before-after" or interrupted time series or time point* or repeated measur*).tw,kf.
44. 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 32 or 37 or 44
46. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
47. Editorial.pt.
48. 46 or 47
49. 45 not 48
50. 14 and 49

Appendix 3. PubMed (epublications ahead of print only)

#1 ((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" OR "random donors" OR protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
#2 (thrombo?ytopheres* OR plateletpheres*)
#3 #1 OR #2
#4 (preoperat*[TI] OR postoperat*[TI] OR perioperat*[TI] OR operation[TI] OR operations[TI] OR operating[TI] OR operated[TI] OR surgery[TI] OR surgical*[TI] OR presurg*[TI] OR postsurg*[TI] OR perisurg*[TI] OR transplant[TI] OR transplants[TI] OR transplanted[TI] OR transplanting[TI] OR transplantation*[TI] OR bypass*[TI] OR arthroplasty*[TI] OR neurosurg*[TI])
#5 #3 AND #4
#6 ((random* OR blind* OR "control group" OR placebo OR "controlled trial" OR "controlled study" OR groups OR trials OR "systematic review" OR "systematic overview" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase OR "time series" OR "repeated measures" OR "before and after" OR "before-after" OR "pre-test" OR "post-test" OR pretest* OR posttest*) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))
#7 #5 AND #6

Appendix 4. Embase (OvidSP)

1. Thrombocyte Transfusion/
2. Thrombocyte/ and transfus*.mp.
3. *Thrombocyte/
4. Thrombo?ytopheresis/
5. ((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.
6. (thrombo?ytopheres* or plateletpheres*).tw.
7. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
8. or/1-7
9. exp Surgery/
10. (preoperat* or postoperat* or perioperat* or operati* or surg* or presurg* or postsurg* or perisurg* or transplant* or bypass* or arthroplasty or neurosurg*).mp.
11. 9 or 10
12. 8 and 11
13. Meta Analysis/
14. Systematic Review/
15. (meta analy* or metaanalys*).tw.
16. ((systematic* or literature) adj2 (review* or overview* or search*)).tw.
17. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.

18. ((electronic* or online) adj (sources or resources or databases)).ab.
19. (additional adj (articles or papers or sources)).ab.
20. (reference lists or bibliograph* or handsearch* or hand search* or manual* search*).ab.
21. (relevant adj (journals or articles)).ab.
22. (search term* or published articles or search strateg*).ab.
23. or/13-22
24. (data extraction or selection criteria).ab.
25. review.pt.
26. 23 or (24 and 25)
27. editorial.pt.
28. 26 not 27
29. randomized controlled trial/ or crossover-procedure/ or single-blind procedure/ or double-blind procedure/ or triple-blind procedure/
30. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or tripl* blind* or assign* or allocat*).tw.
31. (nonrandom* or non random*).tw.
32. (controlled clinical study or controlled study or control group* or trial).tw.
33. controlled clinical trial/
34. time series analysis/
35. epidemiology/
36. pretest posttest control group design/ or pretest posttest design/
37. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw.
38. ((before adj3 after) or "before-after" or interrupted time series or time point* or repeated measur*).tw.
39. or/28-38
40. 12 and 39
41. Animal experiment/ not (human experiment/ or human/)
42. 40 not 41
43. limit 42 to embase

Appendix 5. CINAHL (EBSCOHost)

S1 (MH "Blood Platelets")
S2 TX transfus*
S3 S1 AND S2
S4 (MH "Platelet Transfusion")
S5 (MH "Plateletpheresis")
S6 TX ((platelet* or thrombocyte*) N5 (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*))
S7 TX thrombocytopheres* or plateletpheres*
S8 TX ((platelet* or thrombocyte*) N5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
S9 S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Specialties, Surgical+")
S11 (MH "Surgery, Operative+")
S12 (MH "Perioperative Care+")
S13 TX (surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*)
S14 S10 OR S11 OR S12 OR S13
S15 S9 AND S14
S16 (MH Clinical Trials+)
S17 PT Clinical Trial
S18 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))

S19 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))
S20 TI randomi* OR AB randomi*
S21 MH RANDOM ASSIGNMENT
S22 TI ((phase three) or (phase III)) or AB ((phase three) or (phase III) or (phase three))
S23 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*)))
S24 MH PLACEBOS
S25 MH META ANALYSIS
S26 MH SYSTEMATIC REVIEW
S27 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")
S28 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")
S29 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)
S30 TI placebo* OR AB placebo*
S31 MH QUANTITATIVE STUDIES
S32 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31
S33 (MH "Controlled Before-After Studies") OR (MH "Interrupted Time Series Analysis") OR (MH "Nonrandomized Trials") OR (MH "Pretest-Posttest Design+")
S34 (MH "Quasi-Experimental Studies+") OR (MH "Repeated Measures")
S35 TX (nonrandom* or non random*)
S36 TX (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre N5 post))
S37 TX (controlled clinical study or controlled study or control group*)
S38 TX ((before N3 after) or "before-after" or interrupted time series or time point* or repeated measur*)
S39 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S40 S15 AND S39

Appendix 6. Transfusion Evidence Library

Clinical Specialty: Surgery
Subject Area: Blood Components/Platelets

Appendix 7. LILACS

tw:((platelet OR platelets) AND (prophylactic OR prophylaxis OR transfusion OR transfused OR transfusing OR infused OR infusion OR administered OR required OR needed OR product OR component OR concentrate OR concentrates OR apheresis OR pooled OR donor OR donors OR protocol OR trigger OR threshold OR schedule OR dose OR doses OR dosing OR usage OR utilisation OR utilization)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 8. WEB OF SCIENCE CPC-IS

#1 TS=((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 donor*))
#2 TS=(thrombocytopheres* or plateletpheres*)
#3 TS=((platelet* or thrombocyte*) NEAR/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#4 #3 OR #2 OR #1
#5 TS=(surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*)
#6 #5 AND #4
#7 TS=(random* OR blind* OR "control group" OR placebo OR "controlled trial" OR "controlled study" OR groups OR trials OR "systematic review" OR "systematic overview" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase OR "time series" OR "repeated measures" OR "before and after" OR "before-after" OR "pre-test" OR "post-test" OR pretest* OR posttest*)
#8 #7 AND #6

Appendix 9. ClinicalTrials.gov

Search Terms: (preoperative OR postoperative OR perioperative OR operation OR surgery OR presurgery OR postsurgery OR presurgical OR postsurgical OR transplantation OR bypass OR arthroplasty OR neurosurgery) AND (platelet transfusion OR platelet concentrate)
OR
Search Terms: (preoperative OR postoperative OR perioperative OR operation OR surgery OR presurgery OR postsurgery OR presurgical OR postsurgical OR transplantation OR bypass OR arthroplasty OR neurosurgery)
Interventions: platelet transfusion OR platelet concentrate OR prophylactic platelets

Appendix 10. WHO ICTRP

Title: platelet transfusion OR platelet concentrate
Recruitment Status: ALL
OR
Title: preoperative OR postoperative OR perioperative OR operation OR surgery OR surgical OR presurgery OR postsurgery OR presurgical OR postsurgical OR perisurgical OR transplant OR transplantation OR bypass OR arthroplasty OR neurosurgery
Intervention: platelets OR platelet transfusion OR platelet concentrate OR platelet concentrates
Recruitment Status: ALL

Appendix 11. ROBINS-I

ROBINS-I tool (Stage I)

Specify the review question

Participants	People of all ages with a low platelet count who are due to have surgery
Experimental intervention 1	Prophylactic platelet transfusion before surgery
Control intervention 1	No Prophylactic platelet transfusion before surgery
Control intervention 2	Artificial platelet substitutes for example lyophilised platelets, infusible plasma membranes and liposomes with inserted platelet receptors
Control intervention 3	Cryosupernatant
Control intervention 4	Thrombopoietin (TPO) mimetics
Control intervention 5	Antifibrinolytic drugs
Outcomes	**Primary outcomes** • Mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery. • The number of participants with major procedure-related bleeding within 7 days of surgery, defined as: ○ Surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing, ○ Bleeding of sufficient size to cause delayed wound healing, or wound infection or surgical site bleeding that is unexpected and prolonged or causes haemodynamic instability (as defined by the study) that is associated with a 20g/L drop in Hb ○ Bleeding that requires two or more units of whole blood/red cells within 24h of the bleeding ○ Bleeding that defined by the study with no further details **Secondary outcomes** • The number of participants with minor procedure-related bleeding within 7 days of surgery (e.g. haematoma, prolonged bleeding at surgical site that does not fulfil the definition for major bleeding) • Number of platelet transfusions per participant and number of platelet components per participant • Number of red cell transfusions per participant and number of red cell components per participant • Proportion of participants requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen) within 7 days from the surgery • Quality of life assessment using validated tools • Serious adverse events due to:Transfusion (transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion related infection, transfusion-associated circulatory overload (TACO), transfusion-related dyspnoea) within 24 hours of the transfusion • Surgery (e.g. delayed wound healing, infection) within 30 days after the operation;Length of hospital stay and length of ITU stay • Venous and arterial thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction)

List the confounding areas relevant to all or most studies

We have pre-specified the main potential confounding factors.

- Age ((neonate, child (aged one to 15 years), adult (aged 16 years or older))
- Gender: male:female ratio
- Underlying conditions which caused thrombocytopenia
- Minor surgery or major surgery
- Severity of thrombocytopaenia
- Haemodynamic status at baseline
- Participants with clotting abnormalities, such as disseminated intravascular coagulation (DIC), or concomitant use of anticoagulant or antiplatelet agents
- Previous severe bleeding (e.g. World Health Organization (WHO) grade 3 or 4 or equivalent)

List the possible co-interventions that could be different between intervention groups and could have an impact on outcomes

We have pre-specified the possible co-interventions that could be different between intervention groups and could have an impact on outcomes.

- Receiving corticosteroids
- Intravenous immunoglobulin (IVIG) which usually is given when thrombocytopenia is caused by autoimmune disease
- Pepole with immune thrombocytopenia (ITP) and who had their spleen removed (splenectomy)
- Transfusion of red blood cells
- Transfusion of platelets

The ROBINS-I tool (Stage II): For each study

Specify a target trial specific to the study.

Design	Individually randomised/cluster-randomised/matched
Participants	People of all ages with a low platelet count who are due to have surgery
Experimental intervention	Prophylactic platelet transfusion prior to surgery
Control intervention	No prophylactic platelet transfusion prior to surgery (placebo or no treatment)

Is your aim for this study...?

- ☐ To assess the effect of initiating intervention (as in an intention-to-treat analysis)
- ☐ To assess the effect of initiating and adhering to intervention (as in a per-protocol analysis)

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the 'Summary of findings' table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. risk ratio (RR) = 1.52 (95% confidence interval (CI) 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding area
(i) listed in the review protocol; and
(ii) relevant to the setting of this particular study, or which the study authors identified as potentially important."Important" confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the area, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding areas listed in the review protocol

Confounding area	**Measured Variable (s)**	**Is there evidence that controlling for this variable was unnecessary?***	**Is the confounding area measured validly and reliably by this variable (or these variables)?**	**OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control group?**
			Yes / No / No information	Favour intervention / Favour control / No information

(ii) Additional confounding areas relevant to the setting of this particular study, or which the study authors identified as important

Confounding area	Measured Variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / No / No information	Favour intervention / Favour control / No information

(*Continued*)

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.
"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group?
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group?
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

'Risk of bias' assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study? **If N or PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomised trial There is no NI (No information) option for this signalling question	Y / PY / PN / N
	If Y or PY to 1.1:determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow-up time according to intervention received? If **N or PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y or PY**, proceed to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If **N or PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y or PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required	NA / Y / PY / PN / N / NI
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardisation, and inverse probability weighting. They may control for individual variables or for the esti-	NA / Y / PY / PN / N / NI

(*Continued*)

		mated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding	
	1.5. **If Y or PY to 1.4**: Were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings	NA / Y / PY / PN / N / NI
	1.6. Did the authors control for any post-intervention variables?	Controlling for post-intervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias	NA / Y / PY / PN / N / NI
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-	NA / Y / PY / PN / N / NI

(*Continued*)

		probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present	
	1.8. **If Y or PY to 1.7**: Were confounding areas that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	**Low** - No confounding expected.	Low / Moderate / Serious / Critical / NI
		Moderate - Confounding expected, all known important confounding domains appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	**Moderate** - Confounding expected, all known important confounding domains appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding
		Serious - At least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding	**Serious** - At least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding
		Critical - Confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding	**Critical** - Confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding
	Optional: What is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding do-	Favours experimental / Favours comparator / Unpredictable

(*Continued*)

		mains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact	
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding)	Y / PY / PN / N / NI
	If N or PN to 2.1: go to 2.4		
	2.2. **If Y or PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention and an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome	NA / Y / PY / PN / N / NI
	2.3 **If Y or PY to 2.2:** Were the post-intervention variables that		NA / Y / PY / PN / N / NI

(*Continued*)

	influenced selection likely to be influenced by the outcome or a cause of the outcome?		
	2.4. Do start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow-up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses	Y / PY / PN / N / NI
	2.5.**If Y or PY to 2.2 and 2.3**, or **N or PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow-up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be "No"	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	**Low** - All participants who would have been eligible for the target trial were included in the study and start of follow-up and start of intervention coincide for all participants	Low / Moderate / Serious / Critical / NI
		Moderate - Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow-up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this	**Moderate** - Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow-up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this

(*Continued*)

		was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time	was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time
		Serious - Selection into the study was related to intervention and outcome; or Start of follow-up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time	**Serious** - Selection into the study was related to intervention and outcome; or Start of follow-up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time
		Critical - Selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time	**Critical** - Selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time
	Optional: What is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well- defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, set-	Y / PY / PN / N / NI

(*Continued*)

		ting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'	
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'	Y / PY / PN / N /NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification	Y/ PY / PN / N / NI
	'Risk of bias' judgement	**Low** - Intervention status is well-defined and based solely on information collected at the time of intervention	Low / Moderate / Serious / Critical / NI
		Moderate - Intervention status is well-defined but some aspects of the assignments of intervention status were determined retrospectively	**Moderate** - Intervention status is well-defined but some aspects of the assignments of intervention status were determined retrospectively
		Serious - Intervention status is not well-defined, or major aspects of the assignments of intervention status were determined in a way that could have	**Serious** - Intervention status is not well-defined, or major aspects of the assignments of intervention status were determined in a way that could have

(*Continued*)

		been affected by knowledge of the outcome	been affected by knowledge of the outcome
		Critical - (Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases	**Critical** - (Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to departures from intended interventions	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administering the intervention?	Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, cross-overs to the comparator intervention and switches to another active intervention. We distinguish between analyses where: (1) intervention switches led to follow-up time being assigned to the new intervention, and (2) intervention switches (including cessation of intervention) where follow-up time remained allocated to the original intervention (3) is addressed under time-varying confounding, and should not be considered further here Consider available information on the proportion of study participants who contin-	NA/ Y / PY / PN / N / NI

(*Continued*)

		ued with their assigned intervention throughout follow-up. Was lack of adherence sufficient to impact the intervention effect estimate?	
	4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups	NA/ Y / PY / PN / N / NI
	4.4. **If N or PN to 4.1, 4.2 or 4.3:** Were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	**Low** - No bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued	Low / Moderate / Serious / Critical / NI
		Moderate - Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in	**Moderate** - Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in

(*Continued*)

		the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention	the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention
		Serious - Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses	**Serious** - Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses
		Critical - Substantial deviations from the intended intervention are present and are not adjusted for in the analysis	**Critical** - Substantial deviations from the intended intervention are present and are not adjusted for in the analysis
	Optional: What is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characteris ed either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to missing data	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Miss- ing intervention status may be a problem. This requires that the intended study sample is clear, which it may not be in practice	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on con-	Y / PY / PN / N / NI

(*Continued*)

		founders that were controlled for in the analysis	
	5.4 **If Y or PY to 5.1, 5.2 or 5.3:** Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed	NA / Y / PY / PN / N / NI
	5.5 **If Y or PY to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	**Low** - Data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias	Low / Moderate / Serious / Critical / NI
		Moderate - Proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis	**Moderate** - Proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis
		Serious - Proportions of missing participants differ substan-	**Serious** - Proportions of missing participants differ substan-

(*Continued*)

		tially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis	tially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis
		Critical - (Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis	**Critical** - (Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis
	Optional: What is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer to this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome as-	Y / PY / PN / N / NI

(*Continued*)

		sessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves	
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place	Y / PY / PN / N / NI
	'Risk of bias' judgement	**Low** - The methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status	Low / Moderate / Serious / Critical / NI

(*Continued*)

		Moderate - The methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status	**Moderate** - The methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status
		Serious - The methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status	**Serious** - The methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status
		Critical - The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups	**Critical** - The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from..		

(*Continued*)

	7.1. ... multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomised studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of co-variates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not pre-specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selec-	Y / PY / PN / N / NI

(*Continued*)

		tive reporting on the basis of results	
	'Risk of bias' judgement	**Low** - There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts	Low / Moderate / Serious / Critical / NI
		Moderate - The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined and both internally and externally consistent; and There is no indication of selection of the reported analysis from among multiple analyses; and There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results	**Moderate** - The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined and both internally and externally consistent; and There is no indication of selection of the reported analysis from among multiple analyses; and There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results
		Serious - Outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results	**Serious** - Outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results
		Critical - There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results	**Critical** - There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

(*Continued*)

		towards (or away from) the null, or as being in favour of one of the interventions	
Overall bias	**'Risk of bias' judgement**	**Low** - The study is judged to be at low risk of bias for all domains	Low / Moderate / Serious / Critical / NI
		Moderate - The study is judged to be at low or moderate risk of bias for all domains	**Moderate** - The study is judged to be at low or moderate risk of bias for all domains
		Serious - The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain	**Serious** - The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain
		Critical - The study is judged to be at critical risk of bias in at least one domain	**Critical** - The study is judged to be at critical risk of bias in at least one domain
		No information - There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)	**No information** - There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)
	Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: conceiving the review, protocol development, content expert.
- Reem Malouf: protocol development
- Carolyn Doree: protocol development and search specialist
- Marialena Trivella: protocol development and statistical expert.
- Sally Hopewell: protocol development and methodological expert.
- Janet Birchall: protocol development, content expert

DECLARATIONS OF INTEREST

Lise Estcourt: partly funded by the National Institute of Health Research (NIHR) Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Reem Malouf: partly funded by the National Institute of Health Research (NIHR) Cochrane Programme Grant- Safe and Appropriate Use of Blood Components.

Carolyn Doree: none known.

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

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

Janet Birchall: none known.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK., UK.

To fund the work of the Systematic Review Initiative (SRI)

External sources

- National Institute for Health Research (NIHR) Cochrane Programme Grant, UK., Other.

To provide funding for systematic reviewers and methodological support from the Centre for Statistics in Medicine, Oxford