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Comparison of a therapeutic-only versus prophylactic platelet transfusion policy for people with congenital or acquired bone marrow failure disorders (Protocol)

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[Intervention Protocol]

Comparison of a therapeutic-only versus prophylactic platelet transfusion policy for people with congenital or acquired bone marrow failure disorders

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ABSTRACT

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

To compare a therapeutic-only versus prophylactic platelet transfusion policy for people with myelodysplasia, inherited or acquired aplastic anaemia, and other congenital bone marrow failure disorders.

BACKGROUND

Please see Published notes for an explanation of some technical terms.

Description of the condition

The bone marrow is the site of production of red cells, white cells and platelets from stem cells (termed collectively as haematopoiesis). Bone marrow failure disorders encompass a wide range of diseases that cause quantitative (reduced numbers - cytopenia) or qualitative (reduced function) defects of red cells, white cells and platelets.

Clinical symptoms of people with bone marrow failure disorders are related to the underlying cytopenias (anaemia, neutropenia and thrombocytopenia) that arise from this ineffective haematopoiesis. People can present with fatigue and shortness of breath due to anaemia (low red cell count), recurrent infections due to neutropenia (low neutrophil count, a type of white cell) and bleeding or bruising due to thrombocytopenia (low platelet count). Although anaemia is the most common cytopenia, at least one third of people with conditions like myelodysplastic syndromes (MDS) have moderate or severe thrombocytopenia (Hellstrom-Lindberg 2003). Symptoms due to thrombocytopenia depend not only on the severity of the thrombocytopenia but also any associated comorbidities (coagulation abnormalities, or lesions that are more likely to bleed e.g. peptic ulcer).

Bone marrow failure syndromes can be broadly classified into congenital and acquired disorders.

The most common causes of acquired bone marrow failure are aplastic anaemia and MDS, with MDS being the most commonly diagnosed acquired bone marrow failure in adults (Sekeres 2010). MDS encompasses a diverse group of clonal stem cell disorders that are characterised by dysplasia in one or more cell lines (blood cells have an abnormal shape or size), ineffective haematopoiesis, development of peripheral cytopenias, and an increased risk of developing acute myeloid leukaemia (AML) (Steensma 2006). Overall, the incidence of MDS is estimated at between 2.3 to 4.5 per 100,000 per year (Dinmohamed 2014; Garcia-Manero 2012; Ma 2007; Ma 2012; Neukirchen 2011). However, the incidence increases markedly with age, with the highest incidence in those aged over 80 years (> 30 per 100,000 per year) (Dinmohamed 2014; Ma 2007; Ma 2012; Neukirchen 2011; Rollison 2008). It is also estimated that the incidence of secondary myelodysplasia is increasing because there are a larger number of long-term cancer survivors who have been treated with chemotherapy such as anthracyclines and etoposide that increase the risk of developing myelodysplasia (Le Deley 2007).

Acquired aplastic anaemia is a rare disorder which is characterised by "empty bone marrow" replaced by fat cells. The incidence in Europe and North America is about two per million population per year (Issaragrisil 2006; Montané 2008), whereas the incidence in Asia is higher with estimates ranging from 3.9 to 7.4 cases per million per year (Young 2008). The incidence is unknown in most cases, but environmental factors (industrial chemicals, agricultural pesticides) (Issaragrisil 2006; Young 2008,), drugs (Issaragrisil 2006; Young 2008) and hepatitis viruses (Rauff 2011) have been reported to cause aplastic anaemia. Treatment is tailored to the individual needs of the patient, but involves a combination of supportive care for pancytopenia (reduced numbers of all the cellular elements of blood) (red cell and platelet transfusions, prophylactic antimicrobials), immunosuppressive therapy, and haemopoietic stem cell transplantation. Most patients are not deemed suitable for a haemopoietic stem cell transplant owing to advanced age, co-morbidities or lack of a compatible donor. As a result, supportive management remains the mainstay of treatment.

The inherited bone marrow failure syndromes include Fanconi anaemia, dyskeratosis congenita, Shwachman-Diamond syndrome, Pearson syndrome, congenital amegakaryocytic thrombocytopaenia, familial aplastic anaemia (X-linked and autosomal forms) and Diamond Blackfan anaemia (Shimamura 2009). Fanconi anaemia is the most common inherited bone marrow failure disorder with a reported incidence of approximately one in 360,000 live births and a carrier frequency of one in 300 (Giri 2004). Haematopoietic stem cell transplantation is the definitive treatment in many of these disorders, but supportive therapy in terms of red cell and platelet transfusions are often needed for symptomatic relief, either prior to transplant, or for those patients not suitable to undergo transplant.

Description of the intervention

Despite increasing knowledge about the biology of the underlying diseases, supportive management remains the mainstay of treatment for most people with chronic bone marrow failure disorders. Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in people with thrombocytopenia. Platelet transfusions have an obvious beneficial effect in the management of active bleeding in people with severe thrombocytopenia. However, questions still remain on how this limited resource should be used to prevent severe and life-threatening bleeding. Prophylactic platelet transfusions have been shown to reduce World Health Organization (WHO) Grade 2 or above bleeding in people with haematological malignancies receiving chemotherapy or an allogeneic haematopoietic stem cell transplant (Crighton 2015; Stanworth 2013; Wandt 2012).

The evidence for the use of platelet transfusions to prevent bleeding in people with other conditions is less clear cut (Schiffer 2013; Stanworth 2013; Stanworth 2014; Wandt 2012). International guidelines which consider people with long-term thrombocytopenia recommend either a therapeutic-only strategy (platelet transfusions are given to treat bleeding) (Kaufman 2015; Killick 2014; Liumbruno 2009) or a prophylactic platelet transfusion strategy (platelet transfusions are given when the platelet count falls below a prespecified platelet count threshold (German Medical Association 2014; Killick 2016; NBA 2012; Tinmouth 2007). This threshold is most commonly a platelet count of 5 x 10^9/L (German Medical Association 2014) or 10 x 10^9/L (Bosly 2007; Killick 2016). This threshold can also vary if a person has additional risk factors for bleeding such as sepsis (Killick 2016).

People can become refractory to platelet transfusions (Stanworth 2015). In an analysis of the TRAP 1997 study data, there was a progressive decrease in the post-transfusion platelet count increments and time interval between transfusions as the number of preceding transfusions increased (Slichter 2005). This effect was seen irrespective of whether the patient developed detectable human leukocyte antigen (HLA) antibodies (Slichter 2005). Avoidance of unnecessary prophylactic platelet transfusions is therefore very important in people who are likely to require repeated platelet transfusions over a prolonged period of time because they can become refractory to treatment after repeated transfusions (Hod 2008; Slichter 2005; Stanworth 2015).

Platelet transfusions are associated with adverse events. Mild to moderate reactions to platelet transfusions include rigor, fever, and urticaria (Tinegate 2012). These reactions are not life-threatening but can be extremely distressing for the recipient. Rarer, but more serious sequelae include: anaphylaxis; haemolytic transfusion reactions; transfusion-transmitted infections; transfusion-associated circulatory overload (TACO); and transfusion-related acute lung injury (TRALI) (Blumberg 2010; Kaufman 2015; Raval 2015).

This review does not focus on the absolute need for platelet transfusions in people with chronic bone marrow failure disorders but instead focuses on whether a prophylactic platelet transfusion pol-

icy is required.

How the intervention might work

The morning platelet count is usually used to indicate when a person requires a prophylactic platelet transfusion. In the 1970s it became standard practice to transfuse platelets at platelet counts below 20 x 10^9/L in an attempt to prevent bleeding (Beutler 1993). This practice was partly based on the findings of non-randomised studies that showed that gross haemorrhage (haematuria (blood in the urine), haematemesis (vomiting of blood), and melaena (dark coloured stools)) was present at platelet counts below 5 x 10^9/L more frequently than when the platelet count was between 5 x 10^9/L and 100 x 10^9/L (Gaydos 1962; Slichter 1978). However, these studies did not show any threshold effect at a platelet count of 20 x 10^9/L, nor was any threshold effect seen (Gaydos 1962; Slichter 1978). A threshold of 10x 10^9/L is now considered the standard platelet count threshold (Estcourt 2015; Kaufman 2015; NICE 2015) in people with haematological malignancies who have reversible bone marrow failure after multiple studies confirmed the threshold of 10 x 10^9/L as "safe enough" for prophylactic platelet transfusion (Gmur 1991; Rebulla 1997;Schiffer 2001; Wandt 1998).

For people with chronic bone marrow failure there is much less evidence for the benefit of prophylactic platelet transfusions. A small retrospective study considered platelet transfusion in outpatients with stable chronic severe aplastic anaemia (Sagmeister 1999). Prophylactic platelets were given if the count was 5 x 10^9/L or less. In total 55,239 patient days were reviewed with 18,706 days when the platelet count was 10 x 10^9/L or less. Three major bleeding episodes occurred while participants were on the treatment protocol. The authors concluded that this restrictive policy, with a median transfusion interval of seven days, was feasible, safe and economical.

Only 7.1 x 10^9/L platelets per day are required to maintain vascular integrity and hence, spontaneous bleeding in clinically stable patients is uncommon unless the platelet count is < 5 x 10^9/L (Slichter 2004). A further large study has also shown no relationship between the morning platelet count and the risk of clinically significant bleeding (WHO Grade 2 bleeding) the following day except when the platelet count is very low ($\leq$ 5 x 10^9/L) (Slichter 2010).

A large retrospective review of almost 3000 adults with thrombocytopenia showed no relationship between the morning platelet count, or the lowest platelet count of the day, and the risk of severe or life-threatening bleeding (WHO Grade 3 to 4 bleeding) (Friedmann 2002). This raised the question as to whether a threshold-defined prophylactic platelet transfusion approach is appropriate.

Most recent clinical trials of platelet transfusions have used bleeding as an outcome. An assessment of bleeding is a more clinically-relevant measure of the effect of platelet transfusions than surrogate markers such as the platelet count increment. The definition of what constitutes clinically significant bleeding has varied between studies. Although the majority of more recent platelet transfusion studies now classify it as WHO grade 2 or above, there has been greater heterogeneity in the past (Estcourt 2013; WHO 1979). One limitation of all the scoring systems that have been based on the WHO system is that the categories are relatively broad and subjective. This means that a small change in a patient's bleeding risk may not be detected. Another limitation is that the modified WHO categories are partially defined by whether a bleeding patient requires a blood transfusion. The threshold for intervention may vary between clinicians and institutions and so the same level of bleeding could be graded differently in different institutions. The difficulties with assessing and grading bleeding may limit the ability to compare results between studies and this needs to be kept in mind when reviewing the evidence for the effectiveness of prophylactic platelet transfusions in this review.

Why it is important to do this review

Blood products including platelet components are a valuable and finite resource and their availability depends on the goodwill of voluntary donations. Also, platelet components have a limited shelf life of five to seven days, which makes management of platelet inventories difficult and resource intensive (Fuller 2011; Riley 2012).

As discussed above, the platelet count threshold recommended varies significantly from country to country (German Medical Association 2014; Kaufman 2015; Killick 2014; Killick 2016; Liumbruno 2009). This indicates significant uncertainty among clinicians of the correct management for people with chronic bone marrow disorders.

Our review aims to provide evidence of whether a therapeutic-only platelet transfusion strategy is as effective and safe as a prophylactic platelet transfusion strategy for the prevention of clinically significant or life-threatening bleeding in people with primary bone marrow failure disorders who are thrombocytopenic.

Overall, avoiding the need for unnecessary prophylactic platelet transfusions in people with bone marrow failure disorders will have significant logistical and financial implications for national health services as well as decreasing patients' exposure to the risks of transfusion. It will also have implications on patient's quality of life as it is challenging for patients and caregivers to visit hospital on a regular basis to receive platelet transfusions. The outcomes of this review are perhaps even more important in the development of platelet transfusion strategies in the developing world, where access to blood components is much more limited (Verma 2009).

OBJECTIVES

To compare a therapeutic-only versus prophylactic platelet transfusion policy for people with myelodysplasia, inherited or acquired aplastic anaemia, and other congenital bone marrow failure disorders.

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

Types of participants

We will include all people with long-term bone marrow failure disorders that require platelet transfusions, who are not being actively treated with a haematopoietic stem cell transplant, or intensive chemotherapy. These disorders include myelodysplastic syndromes (MDS), acquired or inherited aplastic anaemia and other congenital bone marrow failure disorders. Due to the inherited nature of a number of bone marrow failure disorders, we will include people of all ages, including neonates.

We will exclude studies of alternatives to platelet transfusion, or studies of people receiving intensive chemotherapy or a stem cell transplant as these are the subjects of separate reviews (Crighton 2015; Desborough 2016).

Types of interventions

Intervention

Participants will receive transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis to treat bleeding (therapeutic platelet transfusions).

Control

Participants will receive prophylactic platelet transfusions and therapeutic platelet transfusions. Prophylactic platelet transfusions are typically given when the platelet count falls below a given trigger level.

There will be no restriction on the dose, frequency, type of platelet component or transfusion trigger of the platelet transfusions, but we will take this information into account in the analysis, where available.

We will include the following comparisons.

- Therapeutic-only platelet transfusions (on-demand triggered by bleeding) versus prophylactic platelet transfusions.
- Placebo versus prophylactic platelet transfusions.

Types of outcome measures

The primary and secondary outcomes of this review are outcomes of interest and we will not use them as inclusion criteria for the assessment of studies.

We will categorise all outcomes according to short-, medium-, and long-term outcomes. We will report the exact definition of these time frames over time periods that are common to as many studies as possible (e.g. up to 30 days, one to six months and greater than six months from the start of the study).

Primary outcomes

- The number of participants with at least one bleeding episode (WHO grade 1 to 4, or WHO grade 2 to 4);
- the total number of days on which bleeding occurred or the total number of bleeding episodes per participant ((WHO grade 1 to 4, or WHO grade 2 to 4);
- the number of participants with at least one episode of severe or life-threatening bleeding;
- time to first bleeding episode from the start of the study (WHO grade 1 to 4, or WHO grade 2 to 4).

Secondary outcomes

- Mortality (all-causes, secondary to bleeding, and secondary to infection);
- 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;
- platelet transfusion interval;
- 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 x days from the start of the study;
- number of hospital admissions and length of hospital stay;
- quality of life assessment using validated tools;
- transfusion-related adverse events (transfusion reactions, transfusion-associated infections, development of platelet antibodies,or platelet refractoriness, thromboembolic events).

Search methods for identification of studies

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

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue) (Appendix 1).
- MEDLINE (OvidSP, 1946 to present) (Appendix 2).
- Embase (OvidSP, 1974 to present) (Appendix 3).
- CINAHL (EbscoHost, 1937 to present) (Appendix 4).
- PubMed (e-publications only) (Appendix 5).
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to present) (Appendix 6).
- LILACS (1980 to present) (Appendix 7).
- IndMed (1986 to present) (Appendix 8).
- PakMediNet (1995 to present) (Appendix 9).
- KoreaMed (1958 to present) (Appendix 9).
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present) (Appendix 10).

We will search for ongoing trials in the following clinical trial registers.

- ClinicalTrials.gov (https://www.clinicaltrials.gov/) (Appendix 11).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) (Appendix 12).

We will apply the sensitivity-maximising Cochrane RCT search filter (Lefebvre 2011) to the MEDLINE search and the SIGN RCT studies filter (www.sign.ac.uk/methodology/filters.html) to Embase and CINAHL. We will not apply any restrictions on date, language or publication status.

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

Searching other resources

We will conduct handsearching of 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 Collaboration methodologies.

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 (AA, AH) 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 title and abstract alone. Additional information will be requested from study authors as necessary to assess the eligibility for inclusion of individual studies. The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, the decision of eligibility will be referred to a third review author (LJE).

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

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (AA, AH) will independently extract data onto standardised forms and perform a cross-check (Higgins 2011a). The data extraction form will be piloted on two included RCTs. The review authors will come to a consensus on the required changes. If an agreement cannot be reached, a third review author (LJE) will be consulted. The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. We will report the characteristics of the included studies in the table of 'Characteristics of included studies'.

The following information will be extracted for each study.

- Source: Study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors 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; setting; number of centres; total study duration; recruitment dates; length of follow-up; power calculation; primary analysis (and definition); stopping rules; method of sequence generation;

allocation concealment; blinding (of clinicians, participants and outcome assessors); any other concerns regarding bias; inclusion and exclusion criteria.

- Characteristics of interventions: Number of study arms; description of experimental arm; description of control arm; and other relevant information.
- Characteristics of participants: Age; gender; primary diagnosis; subgroup classification of primary disease type where appropriate, severity of primary disease, where appropriate, prognostic classification of primary disease where appropriate; additional therapy received; risk of alloimmunisation; baseline haematology laboratory parameters; confounders reported.
- Participant flow: Total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for review outcomes); number of allocated patients who received planned treatment; number of dropouts with reasons (percentage in each arm); protocol violations; missing data.
- Outcomes: number of participants with at least one bleeding episode; total number of days on which bleeding occurred or the total number of bleeding episodes per participant; number of participants with at least one episode of severe or life-threatening bleeding; time to first bleeding episode; mortality (all-causes, secondary to bleeding, and secondary to infection); 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; platelet transfusion interval; 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); quality of life assessment.
- For interventional cohort and pre-post single arm or multiple arms studies we will also collect data if available on: confounding factors, the comparability of groups on confounding factors; 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

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 (AA, AH) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We will report a brief description of the judgement statements upon which the authors have assessed potential bias in the 'Characteristics of Included Studies' table. We will ensure that a consensus on the degree of risk of bias is met through comparison of the review authors' statements and where necessary, through consultation with a third review author (LJE). We will use the Cochrane Collaboration'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?

- Attrition bias

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.

- Reporting bias

We will describe for each included study the possibility of selective outcome reporting bias.

- Other issues

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 studies

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 2014). This tool is based on the Cochrane 'Risk of bias' tool for rating the quality of randomised controlled trials (Higgins 2011c). The tool covers seven domains and the quality of evidence is rated as low, moderate, serious, critical or no information (see Appendix 13 for a copy of the tool), and uses signalling questions for the assessment of the following.

- 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

We will resolve disagreements on the assessment of quality of an included trial by discussion until we reach consensus or failing that by consulting a third review author (LJE).

We have pre-specified the main potential confounding factors.

- Primary diagnosis (aplastic anaemia, myelodysplastic syndromes, congenital bone marrow disorders)
- Age: variability in the age of patients included, e.g. infant (nought to one year) versus paediatric (one to 16 years) versus adult (> 16 years) versus older adult (> 60 years)
- Gender: male to female ratio
- Previous severe bleeding (e.g. WHO grade 3 or 4 or equivalent)
- Use of anticoagulation during study
- Performance status (e.g. Eastern Cooperative Oncology Group (ECOG), Karnofsky Performance Score (KPS))
- Treatment (e.g. azacytidine) versus no treatment (supportive care only)
- Presence of sepsis or infection
- Presence of bleeding disorder

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

- Concomittent use of anti-platelet therapy
- Factor replacements such as fresh frozen plasma (FFP), cryoprecipitate, fibrinogen.
- Use of thrombopoietin (TPO) mimetics (romiplostim, eltrombopag)
- Whole blood transfusions
- Use of steroids or danazol
- Over-the-counter or herbal medicines

Measures of treatment effect

Randomised controlled trials

For continuous outcomes, we will record the mean, standard deviation (SD) 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 mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). It sufficient studies provide HRs, we will use HRs in favour of RRs in a meta-analysis, but for completeness we will also perform a separate meta-analysis of data from studies providing only RRs for the same outcome.

For dichotomous outcomes, we will report the pooled risk ratio (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% CIs (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

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 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-randomised trials, cross-over studies, and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

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 of participants 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

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will analyse the data in RCTs, non-RCTs, and CBA studies separately.

We will evaluate the extent of heterogeneity by visual inspection of forest plots as well as by 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 an I^2 is $\leq$ 50%, moderate if an I^2 is 50% to 80% or considerable if an I^{2is} > 80%. We will use the random-effects model for low-to-moderate heterogeneity. If statistical heterogeneity is considerable, we will not report the overall summary statistic. Potential causes of heterogeneity will be assessed by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

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

Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of the Cochrane Collaboration (Deeks 2011). We will not conduct meta-analyses that include both RCTs and non-RCTs.

Randomised controlled trials

For RCTs where meta-analysis is feasible, we will use the random-effects model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes, or 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

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 not 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

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* (Schunemann 2011a; Schunemann 2011b). The outcomes we will include are listed below in order of most relevant endpoints for patients.

- Number of patients with at least one bleeding episode.
- Total number of bleeding episodes per patient.
- Number of patients with at least one severe or life threatening bleeding episode.
- All-cause mortality.
- Number of units of platelet transfusion per patient.
- Quality of life.
- Transfusion-related adverse events (transfusion reactions, transfusion-associated infections, development of platelet antibodies,or platelet refractoriness, thromboembolic events).

Subgroup analysis and investigation of heterogeneity

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

- Type of bone marrow failure disorder (myelodysplastic syndromes (MDS), aplastic anaemia, congenital bone marrow failure disorder).
- Age of participants grouped as neonatal (nought to one year); paediatric (one to 16 years) adult (17 years to 60 years) elderly adult (greater than 60 years).
- Underlying bleeding tendencies (gastric ulcer, angiodysplasia, acquired coagulopathy etc).
- Concommitant treatment for the underlying disorder (azacytidine).

Sensitivity analysis

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

- Including only those studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation, and in non-RCTs study is judged to be at low risk of bias for all domains).
- Including only those studies with less than a 20% dropout rate.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Hematologic Neoplasms] explode all trees
#2 MeSH descriptor: [Hematologic Diseases] this term only
#3 MeSH descriptor: [Leukemia] explode all trees
#4 MeSH descriptor: [Preleukemia] this term only
#5 MeSH descriptor: [Bone Marrow Diseases] explode all trees
#6 MeSH descriptor: [Thrombocytopenia] explode all trees
#7 MeSH descriptor: [Bone Marrow] this term only and with qualifier(s): [Pathology - PA]
#8 ((myelos* near/2 (nonleukemic or nonleukaemic or non-leukemic or non-leukaemic or aleukemic or aleukaemic)) or (myeloid near/2 metaplasia*) or myelofibros* or (bone marrow near/5 fibros*) or myeloscleros*)
#9 (myelodysplas* or myeloid dysplasia or preleukemi* or preleukaemi* or dysmyelopoie* or 5Q syndrome)
#10 ((aplast* or hypoplast* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic*) near/2 an?emia)
#11 ((haematolog* or hematolog* or hemato-oncolog* or haemato-oncolog*) near/2 patients)
#12 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) near/3 (malignan* or oncolog* or cancer* or neoplasm* or carcinoma*))
#13 erythroid aplasia or erythrodysplas* or hematopoietic aplasia or haematopoietic aplasiapancytopen*
#14 (IMF or PMF or MDS):ti
#15 (bone marrow near/3 (fail* or disease* or disorder* or aplasia or dysplasia or hypoplasia))
#16 (thrombocytop?eni* or leuk?emi* or myelodysplas* or myeloproliferat* or shwachman diamond or (dyskeratosis next congenita*) or AML)
#17 (fanconi* next (an?emia or panmyelopathy or syndrome*))
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 MeSH descriptor: [Blood Platelets] explode all trees
#20 (platelets or thrombocytes):ti
#21 MeSH descriptor: [Platelet Transfusion] explode all trees
#22 MeSH descriptor: [Plateletpheresis] explode all trees
#23 ((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*))
#24 thrombocyt?pheres* or plateletpheres*
#25 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#26 #19 or #20 or #21 or #22 or #23 or #24 or #25
#27 #18 and #26

Appendix 2. MEDLINE (OvidSP) search strategy

1. exp Hematologic Neoplasms/
2. Hematologic Diseases/
3. exp Leukemia/
4. Preleukemia/
5. exp Bone Marrow Diseases/
6. Bone Marrow/pa
7. exp Thrombocytopenia/
8. (bone marrow adj3 (fail* or disease* or disorder* or aplasia or hypoplasia or dysplasia)).tw,kf.
9. (thrombocytop?eni* or thrombop?en* or leuk?emi* or myeloproliferat* or shwachman diamond or (dyskeratosis adj1 congenita*) or AML).tw,kf.
10. (myelodysplas* or myeloid dysplasia or preleukemi* or preleukaemi* or dysmyelopoie* or 5Q syndrome).tw,kf.
11. ((aplast* or hypoplast* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic*) adj2 an?emia).tw,kf.
12. (erythroid aplasia or erythrodysplas* or hematopoietic aplasia or haematopoietic aplasia or pancytopen*).tw,kf.
13. (fanconi* adj (an?emia or panmyelopathy or syndrome*)).tw,kf.
14. ((myelos* adj2 (nonleuk?emic or non-leuk?emic or aleuk?emic)) or (myeloid adj2 metaplasia*) or myelofibros* or (bone marrow adj5 fibros*) or myeloscleros*).tw,kf.
15. (IMF or PMF or MDS).ti.
16. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm*)).tw,kf.
17. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw,kf.
18. or/1-17
19. Platelet Transfusion/
20. Plateletpheresis/
21. (thrombocytopheres* or plateletpheres*).tw,kf.
22. ((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* or unit* or protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
23. platelets.ti.
24. 19 or 20 or 21 or 22 or 23
25. 18 and 24
26. RANDOMIZED CONTROLLED TRIAL.pt.
27. CONTROLLED CLINICAL TRIAL.pt.
28. (randomi* or trial*).tw,kf.
29. (placebo* or randomly or groups).ab.
30. CLINICAL TRIALS AS TOPIC.sh.
31. or/26-30
32. exp COHORT STUDIES/
33. (cohort* or controlled trial or controlled study or comparative trial or comparative study or comparison group or comparator group).tw,kf.
34. ((follow up or observational) adj (study or studies)).tw,kf.
35. (longitudinal* or retrospective* or cross sectional*).tw,kf.
36. CROSS-SECTIONAL STUDIES/
37. CONTROLLED BEFORE-AFTER STUDIES/
38. HISTORICALLY CONTROLLED STUDY/
39. INTERRUPTED TIME SERIES ANALYSIS/
40. (nonrandomi* or non randomi*).tw,kf.
41. “before and after study”.tw,kf.
42. or/32-41
43. Meta-Analysis.pt.
44. (meta analy* or metaanaly*).ab.
45. META-ANALYSIS/

46. or/43-45
47. (studies or trials).ab.
48. 46 and 47
49. (meta analy* or metaanaly*).ti.
50. (systematic* adj2 (review* or overview*)).tw,kf.
51. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citationindex or search terms or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
52. (additional adj (papers or articles or sources)).ab.
53. (electronic adj (sources or resources or databases)).ab.
54. (relevant adj (journals or articles)).ab.
55. "REVIEW LITERATURE AS TOPIC"/
56. META-ANALYSIS AS TOPIC/
57. or/48-56
58. Review.pt.
59. exp CLINICAL TRIALS AS TOPIC/
60. selection criteria.ab. or critical appraisal.ti.
61. (data adj2 (extract* or analys*)).ab.
62. RANDOMIZED CONTROLLED TRIALS/
63. OBSERVATIONAL STUDY/
64. ((cohort* or observational or retrospective*) adj1 (trial* or stud*)).tw,kf.
65. or/59-64
66. 58 and 65
67. 57 or 66
68. (Comment or Letter or Editorial).pt.
69. 67 not 68
70. 31 or 42 or 69
71. exp ANIMALS/ not HUMANS/
72. 70 not 71
73. 25 and 72

Appendix 3. Embase (OvidSP) search strategy

1. Thrombocyte Transfusion/
2. Thrombocytopheresis/
3. ((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 or unit* or protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
4. (thrombocytopheres* or plateletpheres*).tw.
5. (platelets or thrombocytes).ti.
6. or/1-5
7. exp Bone Marrow Disease/
8. Thrombocytopenia/ or Refractory Thrombocytopenia/
9. exp Myelodysplastic Syndrome/
10. Myelodysplasia/
11. exp Preleukemia/
12. Hematologic Malignancy/
13. (bone marrow adj3 (fail* or disease* or disorder* or aplasia or hypoplasia or dysplasia)).tw.
14. ((myelos* adj2 (nonleuk?emic or non-leuk?emic or aleuk?emic)) or (myeloid adj2 metaplasia*) or myelofibros* or (bone marrow adj5 fibros*) or myeloscleros*).tw.
15. (thrombocytop?eni* or thrombop?en* or leuk?emi* or myeloproliferat* or shwachman diamond or (dyskeratosis adj1 congenita*) or AML).tw.
16. (erythroid aplasia or erythrodysplas* or hematopoietic aplasia or haematopoietiic aplasia or pancytopen*).tw.

17. (fanconi* adj (an?emia or panmyelopathy or syndrome*)).tw.
18. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw.
19. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm*)).tw.
20. (myelodysplas* or myeloid dysplasia or preleukemi* or preleukaemi* or dysmyelopoie* or 5Q syndrome).tw.
21. ((aplast* or hypoplast* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic*) adj2 an?emia).tw.
22. (MDS or IMF or PMF).ti.
23. or/7-22
24. 6 and 23
25. Meta Analysis/
26. Systematic Review/
27. (meta analy* or metaanalys*).tw.
28. ((systematic* or literature) adj2 (review* or overview* or search*)).tw.
29. (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.
30. (electronic* adj (sources or resources or databases)).ab.
31. (additional adj (articles or papers or sources)).ab.
32. (reference lists or bibliograph* or handsearch* or hand search* or manual* search*).ab.
33. (relevant adj (journals or articles)).ab.
34. (search term* or published articles or search strateg*).ab.
35. or/25-34
36. (data extraction or selection criteria).ab.
37. review.pt.
38. 35 or (36 and 37)
39. editorial.pt.
40. 38 not 39
41. Controlled Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
42. Randomized Controlled Trial/
43. Randomization/
44. Single Blind Procedure/
45. Double Blind Procedure/
46. Crossover Procedure/
47. Placebo/
48. (randomi* or RCT or placebo*).tw.
49. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
50. ((single or double or triple or treble) adj blind*).tw.
51. Prospective Study/
52. ((crossover* or cross over* or cross-over*) adj2 (trial or study)).tw.
53. or/41-52
54. Case Study/
55. case report$.tw.
56. (note or editorial).pt.
57. or/54-56
58. 53 not 57
59. 40 or 58
60. MAJOR CLINICAL STUDY/
61. LONGITUDINAL STUDY/
62. RETROSPECTIVE STUDY/
63. OBSERVATIONAL STUDY/
64. INTERVENTION STUDY/
65. PROSPECTIVE STUDY/ not RANDOMIZED CONTROLLED TRIAL/
66. COHORT ANALYSIS/
67. COMPARATIVE STUDY/

68. ((follow up or observational* or controlled or comparative) adj2 (trial* or stud*)).tw.
69. ((comparison or comparator) adj group*).tw.
70. (cohort* or retrospective* or longitudinal*).tw.
71. (cross sectional adj (study or studies)).tw.
72. (nonrandomi* or non randomi*).tw.
73. or/60-72
74. 59 or 73
75. 24 and 74

Appendix 4. CINAHL (EbscoHost) search strategy

S1 (MH "Hematologic Neoplasms+")
S2 (MH Leukemia+)
S3 (MH "Anemia, Aplastic+")
S4 (MH "Bone Marrow Diseases+")
S5 (MH Thrombocytopenia+)
S6 (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or leukemi* or leukaemi* or myelodysplas* or myeloproliferat* or myelofibros* or AML or shwachman diamond or (dyskeratosis N1 congenita*))
S7 (myelodysplas* or bone marrow dysplas* or preleukemi* or preleukaemi* or dysmyelopoie* or 5Q syndrome)
S8 ((aplast* or hypoplast* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic*) N2 (anemia or anaemia))
S9 ((myelos* N2 (nonleukemic or nonleukaemic or non-leukemic or non-leukaemic or aleukemic or aleukaemic)) or (myeloid N2 metaplasia*) or myelofibros* or (bone marrow N5 fibros*) or myeloscleros*)
S10 MDS or PMF or IMF or pancytopen* or erythroid aplasia or erythrodysplas* or hematopoietic aplasia
S11 (bone marrow N3 (fail* or disease* or disorder* or aplasia or dysplasia or hypoplasia))
S12 (fanconi* N2 (anemia or anaemia or panmyelopathy or syndrome*))
S13 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) N3 (malignan* or oncolog* or cancer* or neoplasm*))
S14 ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) N2 patients)
S15 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16 (MH "Blood Platelets")
S17 TI (platelet* or thrombocyte*)
S18 (MH "BLOOD TRANSFUSION+")
S19 TI transfus*
S20 S16 OR S17
S21 S18 OR S19
S22 S20 AND S21
S23 (MH "PLATELET TRANSFUSION")
S24 (MH PLATELETPHERESIS)
S25 ((platelet* or thrombocyte*) N5 (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))
S26 (thrombocytopheres* or plateletpheres*)
S27 ((platelet* or thrombocyte*) N5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation))
S28 TI (platelets OR thrombocytes)
S29 S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S30 S15 AND S29
S31 (MH "Prospective Studies+")
S32 (MH "Case Control Studies+")
S33 (MH "Correlational Studies") OR (MH "Cross Sectional Studies")
S34 TI ((cohort study or cohort studies)) OR AB ((cohort study or cohort studies))
S35 TI ((observational stud* or retrospective stud*)) OR AB ((observational stud* or retrospective stud*))
S36 S31 or S32 or S33 or S34 or S35
S37 (MH Clinical Trials+)

S38 PT Clinical Trial
S39 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
S40 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*))
S41 TI randomi* OR AB randomi*
S42 MH RANDOM ASSIGNMENT
S43 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
S44 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*)))
S45 MH PLACEBOS
S46 MH META ANALYSIS
S47 MH SYSTEMATIC REVIEW
S48 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*")
S49 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")
S50 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)
S51 TI placebo* OR AB placebo*
S52 MH QUANTITATIVE STUDIES
S53 S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52
S54 S36 or S53
S55 S30 AND S54

Appendix 5. PubMed (e-publications only) search strategy

#1 (thrombocytop* OR leukemi* OR leukaemi* OR preleuk* OR myelodysplas* OR "bone marrow dysplasia" OR "bone marrow aplasia" OR "bone marrow hypoplasia" OR myeloproliferat* OR myelofibros* OR myeloscleros* OR shwachman diamond OR dyskeratosis congenital OR AML OR dysmyelopoie* OR "5Q syndrome" OR "erythroid aplasia" OR erythrodysplas* OR "hematopoietic aplasia" OR "haematopoietic aplasia" OR pancytopen* OR "bone marrow failure" OR "bone marrow disease" OR "bone marrow diseases" OR "bone marrow disorder" OR "bone marrow disorders" OR "aplastic anemia" OR "aplastic anaemia" OR "hypoplastic anemia" OR "hypoplastic anaemia" OR "refractory anemia" OR "refractory anaemia" OR "sideroblastic anemia" OR "sideroblastic anaemia" OR "aregenerative anemia" OR "aregenerative anaemia" OR "chronic anemia" OR "chronic anaemia" OR fanconi* OR (myelos* AND (nonleukemic OR nonleukaemic or non-leukemic or non-leukaemic or aleukemic or aleukaemic)) OR (myeloid AND metaplasia*) OR ("bone marrow" AND fibros*) OR IMF[TI] OR PMF[TI] OR MDS[TI] OR "haematology patients" OR "hematology patients" OR "haematological patients" OR "hematological patients" OR "haemato-oncology patients" OR "hemato-oncology patients" OR "haemato-oncological patients" OR "hemato-oncological patients")
#2 (((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 "single donors" OR "random donor" OR "random donors" OR protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization)) OR thrombocytopheres* OR plateletpheres* OR platelets[TI] OR thrombocytes[TI])
#3 ((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)
#4 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))
#5 #1 AND #2 AND #3 AND #4

Appendix 6. Transfusion Evidence Library search strategy

All Fields: (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology OR pancytopenia OR bone marrow failure OR bone marrow disease OR bone marrow disorder OR leukemia OR leukaemia OR preleukemia OR preleukaemia OR aplastic OR hypoplastic OR refractory OR sideroblastic OR fanconi OR thrombocytopenia OR thrombocytopenic OR myelodysplasia OR bone marrow dysplasia OR myeloproliferative OR myelofibrosis OR fibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR AML OR dysmyelopoiesis OR 5Q syndrome) AND Subject Area: Platelets
OR
keywords:"Platelet Transfusion" AND (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology OR pancytopenia OR bone marrow failure OR bone marrow disease OR bone marrow disorder OR leukemia OR leukaemia OR preleukemia OR preleukaemia OR aplastic OR hypoplastic OR refractory OR sideroblastic OR fanconi OR thrombocytopenia OR thrombocytopenic OR myelodysplasia OR bone marrow dysplasia OR myeloproliferative OR myelofibrosis OR fibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR AML OR dysmyelopoiesis OR 5Q syndrome)

Appendix 7. LILACS search strategy

tw:((platelet OR thrombocyte OR platelets OR thrombocytes) AND transfusion) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 8. IndMed search strategy

(platelet OR platelets OR thrombocyte OR thrombocytes OR thrombocytopheresis OR plateletpheresis)
AND
(haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology OR pancytopenia OR bone marrow OR leukemia OR leukaemia OR preleukemia OR preleukaemia OR aplastic OR hypoplastic OR refractory OR sideroblastic OR fanconi OR thrombocytopenia OR thrombocytopenic OR myelodysplasia OR myeloproliferative OR myelofibrosis OR fibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR AML OR dysmyelopoiesis OR 5q syndrome)
AND
(randomized OR randomised OR randomly OR blind OR blinded OR trial OR control group OR groups)

Appendix 9. PakMediNet & KoreaMed search strategy

platelet*[ALL] AND "Randomized Controlled Trial" [PT] OR
thrombocyt*[ALL] AND "Randomized Controlled Trial" [PT]

Appendix 10. Web of Science Conference Proceedings Citation Index - Science (CPCI-S) search strategy

Topic: (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology OR pancytopenia OR bone marrow failure OR bone marrow disease OR bone marrow disorder OR leukemia OR leukaemia OR preleukemia OR preleukaemia OR aplastic OR hypoplastic OR refractory OR sideroblastic OR fanconi OR thrombocytopenia OR thrombocytopenic OR myelodysplasia OR bone marrow dysplasia OR myeloproliferative OR myelofibrosis OR fibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR AML OR dysmyelopoiesis OR 5q syndrome)
AND
Topic: (platelet* NEAR/5 transfus*) OR (platelet* NEAR/1 concentrate*)
AND
Topic: (systematic* OR random* OR blind* OR trial* OR control* OR groups)

Appendix 11. ClinicalTrials.gov search strategy

Search Terms: randomized OR randomised OR randomly
Conditions: (hematological malignancies OR hemato-oncology OR bone marrow failure OR pancytopenia OR bone marrow disease OR leukemia OR preleukemia OR aplastic anemia OR hypoplastic anemia OR refractory anemia OR sideroblastic anemia OR fanconi OR thrombocytopenia OR myelodysplasia OR bone marrow dysplasia OR myeloproliferative OR myelofibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR dysmyelopoiesis OR 5Q) Intervention: platelets OR platelet transfusion OR platelet concentrate

Appendix 12. WHO ICTRP search strategy

Title/Condition: (hematological malignancies OR hemato-oncology OR pancytopenia OR bone marrow failure OR pancytopenia OR bone marrow disease OR leukemia OR preleukemia OR aplastic anemia OR hypoplastic anemia OR refractory anemia OR sideroblastic anemia OR fanconi OR thrombocytopenia OR myelodysplasia OR bone marrow dysplasia OR myeloproliferative OR myelofibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR dysmyelopoiesis OR 5Q)
Title/Intervention: platelets OR platelet transfusion OR platelet concentrate

Appendix 13. ROBINS-I (A Cochrane 'Risk of bias' assessment tool: for non-randomised studies of interventions)

ROBINS-I tool (Stage I)

Specify the review question

Participants	All people with long-term bone marrow failure disorders that require platelet transfusions, who are not being actively treated with a haematopoietic stem cell transplant, or intensive chemotherapy. These disorders include myelodysplastic syndromes (MDS), acquired or inherited aplastic anaemia and other congenital bone marrow failure disorders. Due to the inherited nature of a number of bone marrow failure disorders, we will include people of all ages, including neonates
Experimental intervention	Participants will receive transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis to treat bleeding (therapeutic platelet transfusions)
Control intervention	Participants will receive transfusions of platelet concentrates to prevent bleeding in addition to transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis to treat bleeding. Prophylactic platelet transfusions are typically given when the platelet count falls below a given trigger level
Outcomes	Primary outcomes • The number of participants with at least one bleeding episode; • the total number of days on which bleeding occurred or the total number of bleeding episodes per participant; • the number of participants with at least one episode of severe or life-threatening bleeding. • time to first bleeding episode from the start of the study. Secondary outcomes • Mortality (all-causes, secondary to bleeding, and secondary to infection); • number of platelet transfusions per participant and number of platelet components per

(*Continued*)

	participant; • number of red cell transfusions per participant and number of red cell components per participant; • platelet transfusion interval; • 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 x days from the start of the study; • quality of life assessment using validated tools; • transfusion-related adverse events (transfusion reactions, transfusion-associated infections, development of platelet antibodies,or platelet refractoriness, thromboembolic events).

List the confounding areas relevant to all or most studies

We have pre-specified the main potential confounding factors.

- Primary diagnosis (aplastic anaemia, myelodysplastic syndromes, congenital bone marrow disorders)
- 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. WHO grade 3 or 4 or equivalent)
- Use of anticoagulation during study
- Performance Status (e.g. ECOG, KPS)
- Treatment (e.g. azacytidine) versus no treatment (supportive care only)
- Presence of sepsis or infection
- Presence of bleeding disorder

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.

- Concomittent use of anti-platelet therapy
- Factor replacements like fresh frozen plasma, cryoprecipitate, fibrinogen
- Use of TPO mimetics (romiplostim, eltrombopag)
- Whole blood transfusions
- Use of steroids or danazol
- Over-the-counter or herbal medicines

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

Specify a target trial specific to the study.

Design	Individually randomised/cluster randomised/matched
Participants	
Experimental intervention	
Control intervention	

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

(*Continued*)

(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

* 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

(*Continued*)

		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:		

(*Continued*)

	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 estimated 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	NA / Y / PY / PN / N / NI
	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 avail-	NA / Y / PY / PN / N / NI

(*Continued*)

		able. 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	
	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-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present	NA / Y / PY / PN / N / NI
	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 appro-	

(*Continued*)

		priately 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	
		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 domains 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	Favours experimental / Favours comparator / Unpredictable

(*Continued*)

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 influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
	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	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create	NA / Y / PY / PN / N / NI

(*Continued*)

	of selection biases?	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"	
	'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 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	

(*Continued*)

		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, setting, 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'	Y / PY / PN / N / NI
	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	Y / PY / PN / N / NI

(*Continued*)

		control air pollution), the answer to this question is likely to be 'Yes'	
	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	
		Serious - Intervention status is not well- defined, or major aspects of the assignments of intervention status were determined in a way that could have 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	
	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 administer-	Y / PY / PN / N / NI

(*Continued*)

		ing the intervention?	
	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 (1) is addressed under time-varying confounding, and should not be considered further here Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow-up. Was lack of adherence sufficient to impact the intervention effect estimate?	NA/ Y / PY / PN / N / NI
	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 in-	NA / Y / PY / PN / N / NI

(*Continued*)

		tended 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	
	' 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 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	
		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 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	
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?	Missing 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 confounders that were controlled for in the analysis	Y / PY / PN / N / NI
	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 an-	NA / Y / PY / PN / N / NI

(*Continued*)

		swer. 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	
	'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	
		Serious - Proportions of missing participants differ substantially 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	
	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	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	
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 assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves	Y / PY / PN / N / NI
	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 inter-	Y / PY / PN / N / NI

(*Continued*)

		vention-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	
	'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
		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	

(*Continued*)

		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..		
	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 versus change from baseline versus 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 esti-	Y / PY / PN / N / NI

(*Continued*)

		mates 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	
	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 selective reporting on the basis of results	Y / PY / PN / N / NI
	'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	
		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	

(*Continued*)

		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	
	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 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
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	
		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	
		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

Abbreviations

ECOG: Eastern Cooperative Oncology Group;KPS: Karnofsky Performance Score; NRSI: Non-randomied studies of interventions TPO: thrombopoietin

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- Asma Ashraf: protocol development, content expert
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- Carolyn Doree: protocol development and search specialist
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- Marialena Trivella: protocol development and statistical expert.
- Lise Estcourt: conceiving the review, protocol development, content expert.

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Asma Ashraf: none to declare.

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NOTES

Glossary

Allogeneic
The cells (blood cells or stem cells) come from someone other than the patient.
Cytopenia
The reduction of one or more blood cell types.
Dysplasia
Defects in stem cells can cause blood cells to have an abnormal shape or size.
Haematopoiesis
The production of red blood cells, white blood cells, and platelets from stem cells within the bone marrow.