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Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation

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Abstract

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

To determine whether alternative agents (e.g. artificial platelet substitutes, platelet-poor plasma, fibrinogen, rFVIIa, thrombopoietin mimetics) are as effective and safe as the use of platelet transfusions for the prevention of bleeding (prophylactic platelet transfusion) in patients with haematological disorders who are undergoing myelosuppressive chemotherapy or stem cell transplantation. Antifibrinolytics (lysine analogues) will not be included in this review because they have been the focus of another Cochrane review (Wardrop 2013).

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The previous review Estcourt 2012a has now been split into four separate reviews.

BACKGROUND

Description of the condition

Haematological malignancies account for between 8% and 9% of all new cancers reported in the UK and US (CDC 2012; ONS 2012), and their incidence is increasing (11% to 14% increase in new cases of lymphoma and myeloma between 1991 to 2001, and 2008 to 2010) (Cancer Research UK 2013). The prevalence of these disorders is also increasing due to increased survival rates (Coleman 2004; Rachet 2009). These improved survival rates are due to the introduction of intensive chemotherapy treatments and use of stem cell transplantation (Burnett 2011; Fielding 2007; Patel 2009). Over 50,000 haematopoietic stem cell transplants (HSCT) are carried out annually worldwide (Gratwohl 2010), and are used to treat both malignant and non-malignant haematological disorders. Autologous HSCT is the commonest type of HSCT (57% to 59%) (Gratwohl 2010; Passweg 2012). However, chemotherapy and stem cell transplantation can lead to prolonged periods of severe thrombocytopenia (De la Serna 2008; Heddle 2009a; Rysler 2010; Stanworth 2013; Wandt 2012).

Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in thrombocytopenic patients with bone marrow failure secondary to chemotherapy or stem cell transplantation. The ready availability of platelet concentrates has undoubtedly made a major contribution in allowing the development of intensive treatment regimens for haematological disorders (malignant and non-malignant) and other malignancies. The first demonstration of the effectiveness of platelet transfusions was performed in 1910 (Duke 1910). However, it was not until the 1970s and 1980s that the use of platelet transfusions became standard treatment for thrombocytopenic patients with bone marrow failure (Blajchman 2008). Alongside changes in supportive care, the routine use of platelet transfusions in patients with haematological disorders since that time has led to a marked decrease in the number of haemorrhagic deaths associated with thrombocytopenia (Slichter 1980). This has resulted in a considerable increase in the demand for platelet concentrates. Currently, platelet concentrates are the second most frequently used blood component. Administration of platelet transfusions to patients with haematological disorders now constitute a significant proportion (up to 67%) of all platelets issued (Cameron 2007; Greeno 2007; Pendry 2011), and the majority of these (69%) are given to prevent bleeding (Estcourt 2012b).

Patients can become refractory to platelet transfusions. 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 or not patients had developed detectable human leukocyte antigen (HLA) antibodies (Slichter 2005).

Platelet transfusions are also associated with adverse events. Mild to moderate reactions to platelet transfusions include rigors, fever, and urticaria (Heddle 2009b). These reactions are not life-threatening but can be extremely distressing for the patient. Rarer, but more serious sequelae include: anaphylaxis; transfusion-transmitted infections; transfusion-related acute lung injury; and immunomodulatory effects (Benson 2009; Blumberg 2009; Bolton-Maggs

2012; Heddle 2009b; Knowles 2011; Pearce 2011; Popovsky 1985; Silliman 2003; Taylor 2010).

Any strategy that can safely decrease the need for prophylactic platelet transfusions in haematology patients will have significant logistical and financial implications as well as decreasing patients' exposure to the risks of transfusion.

Description of the intervention

Platelet transfusions have an obvious beneficial effect in the management of active bleeding in patients with haematological malignancy and severe thrombocytopenia. However, questions still remain on how this limited resource should be used to prevent severe and life-threatening bleeding (Estcourt 2011). Prophylactic platelet transfusions for patients with chemotherapy-induced thrombocytopenia became standard practice following the publication of several small, randomised controlled trials (RCTs) in the late 1970s and early 1980s (Higby 1974; Murphy 1982; Solomon 1978).

The standard practice in most haematology units across the developed world is to use prophylactic transfusions, in line with guidelines (BCSH 2003; BCSH 2004; Board 2009; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007). The experimental intervention is to give an alternative treatment, such as artificial platelet substitutes, platelet-poor plasma, recombinant factor VIIa (rFVIIa), fibrinogen or thrombopoietin mimetics.

Anti-fibrinolytics (lysine analogues) will not be included in this review because they are the focus of another Cochrane review (Wardrop 2013).

How the intervention might work

Most clinical research has focused on the optimal dose for platelet transfusion or the threshold level of platelet counts for prophylactic platelet transfusions, rather than questioning the underlying assumption that prophylactic platelet transfusions are necessary or effective. The most recent randomised controlled trials (RCTs) have established that many patients develop bleeding at some stage during the period of greatest risk, frequently defined as a period of thrombocytopenia (Heddle 2009a; Slichter 2010). This bleeding covers a spectrum of bleeding, from skin changes to, less commonly, intracranial haemorrhage. In Slichter 2010 patients had similar rates of bleeding (17%) with morning platelet counts within the range of 6 to 80 $\times 10^9$/L. This means that a significant number of bleeding episodes are not being effectively treated by prophylactic platelet transfusions. Treatments that target other parts of the clotting cascade may be as effective at treating bleeding as prophylactic platelet transfusions.

Other means of decreasing the incidence of thrombocytopenic bleeding have been suggested. These include the use of artificial substitutes for platelets, treatment with pharmacological agents that act at different parts of the clotting cascade (Mannucci 1997; Wardrop 2013), and growth factor agonists to stimulate the patient's bone marrow to recover more rapidly and therefore decrease the duration of thrombocytopenia (Miao 2012).

Artificial platelet substitutes

Artificial platelet substitutes overcome some of the problems associated with prophylactic platelet transfusions derived from donors (limited supply and risk of infection). Various different forms have been suggested and studied including liposomes, nanoparticles, nanosheets and hydrogels (Doshi 2012; Nishiya 2002; Okamura 2009a; Okamura 2009b). These have been shown to be effective in in vitro or animal models (Doshi 2012; Nishiya 2002; Okamura 2009a; Okamura 2009b).

Platelet-poor plasma (PPP)

Platelet-poor plasma (PPP) is a source of clotting factor concentrates and fibrinogen.

Recombinant factor VIIa (rFVIIa)

Recombinant factor VIIa (rFVIIa) is licensed for use in patients with haemophilia and inhibitory allo-antibodies, and for prophylaxis and treatment of patients with congenital factor VII deficiency. It is also used for off-license indications to prevent bleeding in operations where blood loss is likely to be high, and/or to stop bleeding that is proving difficult to control by other means. However, a recent systematic review showed that the effectiveness of rFVIIa outside its licensed indications remains unproven (Simpson 2012).

Fibrinogen

Fibrinogen is the endogenous substrate for fibrin formation (Manco-Johnson 2009). The formation of a fibrin network, formed by activated platelets and cross-linked fibrin strings, is the endpoint of the coagulation process in-vivo (Sorensen 2011). Multiple in vitro experiments, animal studies, and non-randomised clinical studies have suggested that use of a fibrinogen concentrate may be efficient and safe in controlling perioperative bleeding (Solomon 2009; Sorensen 2011).

Desmopressin

Desmopressin (DDAVP), a derivative of the anti-diuretic hormone, has been used since the 1970s to treat mild haemophilia A and von Willebrand’s disease without the need for blood products (Mannucci 1997). DDAVP increases the plasma levels of factor VIII (FVIII) and von Willebrand factor (vWF) and enhances platelet adhesion to the vessel wall but has no effect on the platelet count (Barnhart 1983; Mannucci 1997; Sakariassen 1984). It has been shown to be effective at preventing bleeding in patients who have normal levels of FVIII and vWF, e.g. patients with uraemia (Mannucci 1997).

Thrombopoietin mimetics

Thrombopoietin (TPO) is the major regulator of both megakaryopoeisis and thrombopoiesis, it promotes cell differentiation and prevents apoptosis of megakaryocyte colony-forming cells and early megakaryocyte progenitors (Kuter 2010). The two main TPO mimetics in current use are romiplostim (weekly injection) and eltrombopag (daily oral tablet). Romiplostim is recommended by the National Institute for Clinical Excellence (NICE) for use in adults with immune thrombocytopenia (ITP) who have severe disease and a high risk of bleeding (NICE 2011) but eltrombopag is not (NICE 2010). However, in a recent

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systematic review of TPO receptor agonists in chronic ITP there was no evidence to demonstrate that TPO receptor agonists improved significant bleeding events despite significantly increasing platelet response (Zeng 2011).

Assessment of bleeding

A bleeding assessment has been seen as a more clinically relevant measure of the effect of platelet transfusions than surrogate markers such as platelet increment.

Any review that uses bleeding as a primary outcome measure needs to assess the way that the trials have recorded bleeding. Unfortunately, the way bleeding has been recorded and assessed has varied markedly between trials (Cook 2004; Estcourt 2013a; Heddle 2003).

Retrospective analysis of bleeding leads to a risk of bias because bleeding events may be missed, and only more severe bleeding is likely to have been documented. Prospective bleeding assessment forms provide more information and are less likely to miss bleeding events. However, different assessors may grade the same bleed differently and it is very difficult to blind the assessor to the intervention.

The majority of trials have used the World Health Organization (WHO) system, or a modification of it, for grading bleeding (Estcourt 2013a; Koreth 2004; 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 definition of what constitutes clinically significant bleeding has varied between studies. Although the majority of more recent platelet transfusion studies (Heddle 2009a; Slichter 2010; Stanworth 2010; Wandt 2012) now classify it as WHO grade 2 or above there has been greater heterogeneity in the past (Cook 2004; Estcourt 2013a; Koreth 2004). 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.

Why it is important to do this review

Although considerable advances have been made in platelet transfusion therapy in the last 40 years, 3 major areas continue to provoke debate.

- Firstly, what is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?
- Secondly, which threshold should be used to trigger the transfusion of prophylactic platelets?
- Thirdly, are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention and/or control of life-threatening thrombocytopenic bleeding?

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The initial formulation of this Cochrane review attempted to answer these questions, but there was insufficient evidence available at the time for any definitive conclusions to be drawn (Stanworth 2004).This review was updated (Estcourt 2012a). However, for clarity and simplicity this review has now been split to answer each question separately.

This review will focus on the additional question of whether alternative agents instead of prophylactic platelet transfusions can be used for the prevention and/or control of life-threatening thrombocytopenic bleeding.

This review will not assess the evidence for antifibrinolytics (lysine analogues) as this is the focus of a recent review (Wardrop 2013). Avoiding the need for unnecessary prophylactic platelet transfusions in haematology patients will have significant logistical and financial implications for national health services as well as decreasing patients' exposure to the risks of transfusion. This knowledge is 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).

The three questions above will be assessed by three further separate reviews.

This review will not assess whether there are any differences in the efficacy of apheresis versus whole-blood derived platelet products, the efficacy of pathogen-reduced platelet components, the efficacy of HLA-matched versus random donor platelets, or differences between ABO identical and ABO non-identical platelet transfusions. This is because these topics have been covered by recent systematic reviews (Butler 2013; Heddle 2008; Pavenski 2013; Shehata 2009).

OBJECTIVES

To determine whether alternative agents (e.g. artificial platelet substitutes, platelet-poor plasma, fibrinogen, rFVIIa, thrombopoietin mimetics) are as effective and safe as the use of platelet transfusions for the prevention of bleeding (prophylactic platelet transfusion) in patients with haematological disorders who are undergoing myelosuppressive chemotherapy or stem cell transplantation. Anti-fibrinolytics (lysine analogues) will not be included in this review because they have been the focus of another Cochrane review (Wardrop 2013).

METHODS

Criteria for considering studies for this review

Types of studies—We will include randomised controlled trials (RCTs). There will be no restrictions on language or publication status.

Types of participants—Patients with haematological disorders receiving treatment with myelosuppressive chemotherapy and/or stem cell transplantation. We will include people of all ages, and we will include both inpatients and outpatients.

If trials consist of mixed populations of patients, e.g. those with diagnoses of solid tumours, only data from the haematological subgroups will be used. If subgroup data for

haematological patients is not provided (after contacting the authors of the trial), the trial will be excluded if fewer than 80% of participants have a haematological disorder. Any patients that are not being treated with intensive chemotherapy or a stem cell transplant will be excluded. We will include patients with non-malignant haematological disorders (e.g. aplastic anaemia, congenital bone marrow failure syndromes) that are being treated with an allogeneic stem cell transplant.

Types of interventions—We will include the two following comparisons:

1. Alternative agent versus prophylactic platelet transfusion
2. Alternative agent and prophylactic platelet transfusion versus placebo or no treatment and prophylactic platelet transfusion

We will consider the following interventions:

- Experimental intervention: alternative agents
  - artificial platelet substitutes
  - platelet-poor plasma
  - rFVIIa
  - fibrinogen
  - TPO mimetics
  - desmopressin

There will be no restriction on the dose of alternative agents used.

- Comparator intervention:
  - Comparison 1: alternative agent versus prophylactic platelet transfusion. The comparator is prophylactic platelet transfusions. Transfusion of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given prophylactically to prevent bleeding. Prophylactic platelet transfusions are typically given when blood platelet counts fall below a given trigger level. There will be no restriction on the dose or frequency of platelet transfusions, nor will there be a restriction on the transfusion trigger level, although we will take this information into account in the analysis where available.
  - Comparison 2:alternative agent and prophylactic platelet transfusion versus placebo or no treatment and prophylactic platelet transfusion. The comparator is prophylactic platelet transfusions and placebo or no treatment. There will be no restriction on the dose or frequency of platelet transfusions used in addition to the alternative agents, but the dose of prophylactic platelet transfusions received and the platelet transfusion threshold at which they are given will be the same in both arms of the study.

Types of outcome measures

Primary outcomes: Number and severity of bleeding episodes within 30 days from the start of the study:

- The number of patients with at least one bleeding episode.
- The total number of days on which bleeding occurred per patient.
- The number of patients 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) within 30 days and 90 days from the start of the study.
- Number of platelet transfusions per patient and number of platelet components per patient within 30 days from the start of the study.
- Number of red cell transfusions per patient and number of red cell components per patient within 30 days from the start of the study.
- Platelet transfusion interval within 30 days from the start of the study.
- Proportion of patients requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate) within 30 days from the start of the study.
- Overall survival within 30 days, 90 days, and 180 days from the start of the study.
- Duration of thrombocytopenia within 30 days from the start of the study.
- Proportion of patients achieving complete remission within 30 days and 90 days from the start of the study.
- Total time in hospital within 30 days from the start of the study.
- Adverse effects of treatments (transfusion reactions, transfusion-transmitted infections, thromboembolism, development of platelet antibodies, development of platelet refractoriness, drug reactions) within 30 days and 90 days from the start of the study.
- Quality of life, as defined by the individual studies.

We will express all primary and secondary outcomes in the formats defined in the Measures of treatment effect section of this protocol if data are available. Two of our outcomes are of special note as we expect them to be only narrative reports. Firstly, assessment of quality of life will use the study's own measure as there is no definitive patient reported outcome measure for this patient group (Estcourt 2013b). Secondly, the platelet transfusion interval can be calculated in many different ways and it is unlikely that the exact methodology will be reported sufficiently to allow us to combine the data.

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Search methods for identification of studies

The Systematic Review Initiative (SRI) Information Specialist (CD) formulated entirely new search strategies for this review in collaboration with the Cochrane Haematological Malignancies Review Group.

Electronic searches

Bibliographic databases: We will search for randomised controlled trials in the following databases:

- CENTRAL (*The Cochrane Library*) (Appendix 1)
- MEDLINE (Ovid, 1946 to the present) (Appendix 2)
- PubMed (epublications only) (Appendix 3)
- Embase (Ovid, 1974 to the present) (Appendix 4)
- CINAHL (EBSCOhost, 1982 to the present) (Appendix 5)
- UKBTS/SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to the present) (Appendix 6)
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to the present) (Appendix 7)
- Lilacs (BIREME/PAHO/WHO, 1982 to the present) (Appendix 8)
- IndMed (ICMR-NIC, 1985 to the present) (Appendix 9)
- KoreaMed (KAMJE, 1997 to the present) (Appendix 10)
- PakMediNet (2001 to the present) (Appendix 10)

As the search strategies have been rewritten, searches will be run from the earliest dates specified above and will not be updated from the original and updated searches in January 2002 (Stanworth 2004) and November 2011 (Estcourt 2012a). Searches in MEDLINE, Embase and CINAHL will be combined with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). All search strategies are presented in the Appendices as indicated.

Databases of ongoing trials: We will also search ClinicalTrials.gov (http://clinicaltrials.gov/ct2/search) (Appendix 11), the WHO International Clinical Trials Registry (ICTRP) (http://apps.who.int/trialsearch/) (Appendix 11), the ISRCTN Register (http://www.controlled-trials.com/isrctn/) (Appendix 12), the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search) (Appendix 13) and the Hong Kong Clinical Trials Register (http://www.hkclinicaltrials.com/) (Appendix 14) in order to identify ongoing trials.

Searching other resources

Handsearching of references: We will check references of all included trials, relevant review articles, and current treatment guidelines for further literature. These searches will be limited to the ‘first generation’ reference lists.

Personal contacts: We will contact authors of relevant studies, study groups and experts worldwide known to be active in the field for unpublished material or further information on ongoing studies.

Data collection and analysis

Selection of studies: The selection of studies will be updated from the selection of studies performed for the previous version of this review (Estcourt 2012a).

Two independent review authors (LE, RG) will initially screen all electronically-derived citations and abstracts of papers identified by the review search strategy for relevance. Studies clearly irrelevant will be excluded at this stage.

The full texts of all potentially-relevant trials will then formally be assessed for eligibility by two independent review authors (LE, RG) against the criteria outlined above. All disagreements will be resolved by discussion with a third review author (SS). Further information will be sought from study authors if the article contains insufficient data to make a decision about eligibility. A study eligibility form will be designed for trials of platelet transfusion to help in the assessment of relevance, which will include ascertaining whether the participants had haematological disorders, and whether the two groups could be defined in the trial on the basis of use of an alternative agent to prophylactic platelet transfusions. The reasons why potentially-relevant studies failed to meet the eligibility criteria will be recorded.

Data extraction and management—The data extraction will be updated from the data extraction performed for the previous version of this review (Estcourt 2012a). This will include data extraction for all studies that have been included since the previous review and also for all review outcomes that were not part of the previous review (e.g. platelet transfusion interval, quality of life).

Two review authors (LE, RG) will conduct data extraction according to the guidelines proposed by the Cochrane Collaboration (Higgins 2011a). Potential disagreements between the review authors will be resolved by consensus. The review authors will not be blinded to names of authors, institutions, journals, or the outcomes of the trials. The data extraction forms have been piloted in the previous version of this review (Estcourt 2012a). Due to minor changes in the format the forms will piloted on a further study, thereafter the two authors (LE, RG) will extract data independently for all the studies. The following data will be extracted:

General information: Review author's name, date of data extraction, study ID, reference manager number, first author of study, author's contact address (if available), citation of paper, objectives of the trial.

Trial details: Trial design, location, setting, sample size, power calculation, treatment allocation, randomisation, blinding, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

Characteristics of participants: Age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of haematological disease, lost to follow-up numbers, drop outs (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment, prognostic factors.

Interventions: Experimental and control interventions, type of platelet given, timing of intervention, dosage of platelet given, compliance to interventions, additional interventions given especially in relation to red cell transfusions, any differences between interventions.

Assessment of bias: Sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.

Outcomes measured: Number and severity of bleeding episodes. Mortality (all causes), and mortality due to bleeding. Proportion of patients achieving complete remission. Disease-free survival. Time in hospital. Number of platelet transfusions and platelet components. Number of red cell transfusions and red cell components. Platelet transfusion interval. Proportion of patients requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate). Duration of thrombocytopenia. Quality of life. Adverse effects of treatments (e.g. transfusion reactions, transfusion-transmitted infections, thromboembolism, development of platelet antibodies or platelet refractoriness).

Both full-text versions and abstracts will be used to retrieve the data. Publications reporting on more than one trial will be extracted using one data extraction form for each trial. Trials reported in more than one publication will be extracted on one form only. If these sources do not provide sufficient information, we will contact the authors, study groups or companies for additional details.

Data entry into software will be done by one review author and will be checked for accuracy by a second review author.

Assessment of risk of bias in included studies—The ‘Risk of bias’ assessment will be updated from the ‘Risk of bias’ assessment performed for the previous version of this review (Estcourt 2012a).

Two review authors (LE, RG) will assess all newly-included studies for possible risk of bias (as described in the *Cochrane Handbook* (Higgins 2011c)). The assessment will include information about the design, conduct and analysis of the trial. Each criterion will be evaluated on a three-point scale: low risk of bias, high risk of bias, or unclear. To assess risk of bias, the following questions will be included in the risk of bias table for each included study:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?

- Was knowledge of the allocated intervention adequately prevented during the study (including an assessment of blinding of participants, personnel, and outcome assessors)?
- Were incomplete outcome data adequately addressed (for every outcome separately)?
- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect—For dichotomous outcomes the number of outcomes in the treatment and control groups will be recorded and the treatment effect measures across individual studies will be estimated as the relative effect measures (relative risk (RR) with 95% confidence intervals (CI)).

For continuous outcomes, the mean and standard deviations will be recorded. For continuous outcomes measured using the same scale of the effect measure will be the mean difference (MD) with 95% confidence intervals, or the standardised mean difference (SMD) for outcomes measured using different scales. For time-to-event outcomes we will extract the hazard ratio (HR) from published data according to Parmar 1998 and Tierney 2007.

If appropriate, the number needed to treat to benefit (NNTB) with CIs and the number needed to treat to harm (NNTH) with CIs will be reported.

If the data available cannot be reported in any of the formats described above a narrative report will be performed.

Dealing with missing data—Missing data will be dealt with according to the recommendations in the *Cochrane Handbook* (Higgins 2011b). We will contact authors in order to obtain information that is missing or unclear in the published report.

In trials that include patients with haematological disorders as well as patients with solid tumours or non-malignant haematological disorders, we will extract data for the malignant haematology subgroup from the general trial data. If this cannot be done the trial author will be contacted.

Within an outcome, when there are missing data, the preferred analysis will be an intention-to-treat analysis (ITT). The number of patients lost to follow-up will be recorded for each trial.

Assessment of heterogeneity—If studies are considered sufficiently homogenous in their study design, we will conduct a meta-analysis and assess the statistical heterogeneity (Deeks 2011). Statistical heterogeneity of treatment effects between trials will be assessed using a Chi^2 test with a significance level at $P < 0.1$. The I^2 statistic will be used to quantify possible heterogeneity ($I^2 > 50\%$ moderate heterogeneity, $I^2 > 80\%$ considerable heterogeneity). Potential causes of heterogeneity will be explored by sensitivity and subgroup analyses if possible.

Assessment of reporting biases—We will explore meta-analyses with at least 10 trials for potential publication bias (small trial bias) by generating a funnel plot, and statistically test using a linear regression test. We will consider a P value of less than 0.1 significant for this test (Sterne 2011).

Data synthesis—Analyses will be performed according to the recommendations of the Cochrane Collaboration (Deeks 2011). Aggregated data will be used for analysis. For statistical analysis, we will enter data into Review Manager 2012.

Where meta-analysis is feasible, we will use the fixed-effect model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method for continuous outcomes. The generic inverse variance method will be employed for time-to-event outcomes.

We will use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity. If heterogeneity, as expressed by the I^2, is found to be above 50%, both the fixed-effect and random-effects models will be reported. If heterogeneity is found to be above 80%, we will not perform a meta-analysis and results will be commented on as a narrative.

GRADEprofiler will be used to create ‘Summary of findings’ tables as suggested in the *Cochrane Handbook* (Schünemann 2011). This will include the number and severity of bleeding episodes within 30 days from the start of the study (number of patients with at least one bleeding episode; number of days on which bleeding occurred; number of patients with severe or life-threatening bleeding; time to first bleeding episode), number of platelet transfusions within 30 days from the start of the study, 30 day mortality and quality of life.

Separate meta-analyses will performed for each type of alternative agent.

Subgroup analysis and investigation of heterogeneity—Two subgroup analyses have been pre-specified prior to the previous version of this review; these are fever and patients’ diagnostic and treatment subgroups. We will consider performing subgroup analysis on the following characteristics, if appropriate:

- Presence of fever (> 38°C)
- Underlying disease
- Type of treatment (autologous HSCT, allogeneic HSCT, or chemotherapy alone)
- Age of the patient (paediatric, adults, older adults (> 60 years))

Meta-regression will be performed if subgroups contain more than 10 studies (Deeks 2011). Differences between subgroups will be compared using a random-effects model when the two subgroups are independent following the guidance in Chapter 9 of the *Cochrane Handbook* (Deeks 2011). If this is not possible then differences will be commented on as a narrative.

Investigation of heterogeneity between studies will also include, if appropriate:

- Age of the study (as the type of platelet component has changed over the last 40 years)
- Different platelet component doses
- Different prophylactic platelet transfusion thresholds

Sensitivity analysis—Robustness of the overall results will be assessed by sensitivity analysis with respect to those trials deemed to be at high risk of bias.

For dichotomous data, we will assess the influence of participant drop-out, analysing separately RCTs with less than 20% drop-out, RCTs with 20% to 50% drop-out and RCTs with greater than 50% drop-out.

We will use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity.

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Appendix 1. CENTRAL (The Cochrane Library) search strategy

#1	MeSH descriptor: [Hematologic Neoplasms] explode all trees
#2	MeSH descriptor: [Leukemia] explode all trees
#3	MeSH descriptor: [Lymphoma] explode all trees
#4	MeSH descriptor: [Multiple Myeloma] explode all trees
#5	MeSH descriptor: [Anemia, Aplastic] explode all trees
#6	MeSH descriptor: [Bone Marrow Diseases] explode all trees
#7	MeSH descriptor: [Thrombocytopenia] explode all trees
#8	(thrombocytop* or leukemi* or leukaemi* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or

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polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)

#9 ((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*))

#10 MeSH descriptor: [Antineoplastic Agents] explode all trees

#11 MeSH descriptor: [Stem Cell Transplantation] explode all trees

#12 MeSH descriptor: [Bone Marrow Transplantation] this term only

#13 MeSH descriptor: [Radiotherapy] explode all trees

#14 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)

#15 ((haematolog* or hematolog* or hemato-oncolog* or haemato-oncolog*) near/2 patients)

#16 (malignan* or oncolog* or cancer*):ti

#17 #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

#18 MeSH descriptor: [Factor VIIa] explode all trees

#19 (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or eptacog* or proconvertin)

#20 ((activated near/2 factor seven) or (activated near/2 factor vii) or (activated near/3 rfvii) or (activated near/2 fvii))

#21 (factor seven or factor vii or factor 7):ti

#22 MeSH descriptor: [Fibrinogen] explode all trees

#23 (“fibrinogen NEXT concentrate*” or “factor I” OR haemocomplettan* OR octafibrin* OR riastap*)

#24 ((platelet* or thrombocyte*) near/5 (substitute* or artificial*))

#25 platelet-poor plasma*

#26 MeSH descriptor: [Deamino Arginine Vasopressin] explode all trees

#27 (desmopressin* or vasopressin deamino or nocutil or octim or minurin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or ddavp or ddavp or adiuretin or octostim or desmogalen)

#28 MeSH descriptor: [Thrombopoietin] explode all trees and with qualifiers: [Administration & dosage - AD, Adverse effects - AE, Therapeutic use - TU]

#29 MeSH descriptor: [Recombinant Fusion Proteins] explode all trees and with qualifiers: [Administration & dosage - AD, Adverse effects - AE, Therapeutic use - TU]

#30 MeSH descriptor: [Receptors, Fc] explode all trees and with qualifiers: [Administration & dosage - AD, Therapeutic use - TU]

#31 MeSH descriptor: [Receptors, Thrombopoietin] explode all trees and with qualifiers: [Administration & dosage - AD, Agonists - AG, Therapeutic use - TU]

#32 (eltrombopag* or promacta* or revolade* or romiplastin* or romiplostim* or nplate)

#33 (amg531 or amg 531 or amg-531 or sb497115 or sb 497115 or sb-497115 or fab59 or fab 59 or fab-59 or AKR501 or AKR 501 or AKR-501 or YM477 or YM 477 or YM-477 or Peg-TPOmp*)

#34 ((TPO or thrombopoietin) next (mimetic* or receptor agonist* or agonist* or agent*))

#35 (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) near/5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*))

#36 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR # 32 OR #33 OR #34 OR #35

#37 #17 AND #36

Appendix 2. MEDLINE (Ovid) search strategy

1. exp Hematologic Neoplasms/
2. exp Leukemia/or exp Lymphoma/
3. exp Multiple Myeloma/
4. exp Anemia, Aplastic/
5. exp Bone Marrow Diseases/
6. exp Thrombocytopenia/
7. (thrombocytop* or leukemi* or leukaemi* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
8. ((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.
9. exp Antineoplastic Agents/
10. exp Stem Cell Transplantation/or Bone Marrow Transplantation/or exp Radiotherapy/
11. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*).tw.

12. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw.
13. (malignan* or oncolog* or cancer*).ti.
14. or/1-13
15. Factor VIIa/
16. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or eptacog* or proconvertin).tw.
17. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw.
18. (factor seven or factor vii or factor 7).ti.
19. Fibrinogen/ad, ae, sd, tu, th
20. *Fibrinogen/
21. (fibrinogen concentrate* or factor I OR haemocomplettan* OR octafibrin* OR riastap*).tw.
22. ((platelet* or thrombocyte*) adj5 (substitute* or artificial*)).tw.
23. platelet-poor plasma*.tw.
24. *Deamino Arginine Vasopressin/
25. Deamino Arginine Vasopressin/ad, ae, st, tu, to
26. (desmopressin* or vasopressin deamino or nocutil or octim or minurin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or ddavp or ddavp or adiuretin or octostim or desmogalen).tw.
27. Thrombopoietin/ad, tu
28. Recombinant Fusion Proteins/ad, tu
29. Receptors, Fc/ad, tu
30. Receptors, Thrombopoietin/ad, ag, tu
31. (eltrombopag* or promacta* or revolade* or romiplastin* or romiplostim* or nplate or TPO*).tw.
32. (amg531 or amg 531 or amg-531 or sb497115 or sb 497115 or sb-497115 or fab59 or fab 59 or fab-59 or AKR501 or AKR 501 or AKR-501 or YM477 or YM 477 or YM-477 or Peg-TPOmp*).tw.
33. ((TPO or thrombopoietin) adj (mimetic* or receptor agonist* or agonist* or agent*)).tw.
34. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw.

35. or/15-34

36. 14 and 35

Appendix 3. PUBMED (epublications only)

#1 (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR multiple myeloma OR plasma cell myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR Hodgkin*)

#2 ((haematolog* OR hematolog* OR blood OR red cell* OR white cell* OR lymphom* OR marrow OR platelet*) AND (malignan* OR oncolog* OR cancer OR cancers OR neoplasm*))

#3 #1 OR #2

#4 ("factor viia"[TI] OR "factor 7a"[TI] OR rfviia[TI] OR fviia[TI] OR novoseven*[TI] OR "novo seven*"[TI] OR eptacog*[TI] OR proconvertin[TI] OR "fibrinogen concentrate*"[TI] OR "factor I"[TI] OR haemocomplettan[TI] OR octafibrin[TI] OR riastap[TI])

#5 "activated factor seven"[TI] OR "activated factor vii"[TI] OR "activated rfvii"[TI] OR "activated fvii"[TI]

#6 (factor seven[TI] OR factor vii[TI] OR factor 7[TI])

#7 ((platelet* OR thrombocyte*) AND (substitute* OR artificial*))

#8 (platelet-poor plasma* OR desmopressin* OR vasopressin deamino OR nocutil OR octim OR minurin OR deamino-8-d-arginine vasopressin OR vasopressin 1-desamino-8-arginine OR desmotabs OR ddavp OR ddavp OR adiuretin OR octostim OR desmogalen)

#9 (eltrombopag* OR promacta* OR revolade* OR romiplastin* OR romiplostim* OR nplate*)

#10 (amg531 OR amg 531 OR amg-531 OR sb497115 OR sb 497115 OR sb-497115 OR fab59 OR fab 59 OR fab-59 OR AKR501 OR AKR 501 OR AKR-501 OR YM477 OR YM 477 OR YM-477 OR Peg-TPOmp*)

#11 ((TPO OR thrombopoietin) AND (mimetic* OR receptor agonist* OR agonist* OR agent*))

#12 ((haemosta* OR hemosta* OR antihaemorrhag* OR antihemorrhag* OR anti haemorrhag* OR anti-hemorrhag*) AND (drug OR drugs OR agent* OR treatment* OR therapy OR therapies)) OR (coagulat* factor OR clotting factor OR coagulat* factors OR clotting factors))

#13 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 #3 AND #13

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#15 (random* OR blind* OR control group* OR placebo OR controlled trial OR controlled study OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature OR medline OR cochrane OR embase) AND (publisher[sb] NOT pubstatusnihms)

#16 #14 AND #15

Appendix 4. EMBASE (Ovid) search strategy

1. Hematologic Malignancy/
2. Lymphoma/
3. NonHodgkin Lymphoma/
4. Hodgkin Disease/
5. exp Myeloproliferative Disorder/
6. exp Aplastic Anemia/
7. exp Thrombocytopenia/
8. (thrombocytop* or leukemi* or leukaemi* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
9. ((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.
10. exp Chemotherapy/
11. exp Stem Cell Transplantation/
12. exp Bone Marrow Transplantation/
13. exp Radiotherapy/
14. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*).tw.
15. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw.
16. (malignan* or oncolog* or cancer*).ti.
17. or/1-16
18. Factor VIIa/
19. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or eptacog* or proconvertin).tw.
20. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw.

21. (factor seven or factor vii or factor 7).ti.
22. Fibrinogen/ae, ct, ad, cb, cm, cr, dv, do, dt, to, iv, pa, sc, th
23. Fibrinogen Concentrate/
24. (fibrinogen concentrate* or factor I or haemocomplettan* OR octafibrin* OR riastap*).tw.
25. ((platelet* or thrombocyte*) adj5 (substitute* or artificial*)).tw.
26. platelet-poor plasma*.tw.
27. *Desmopressin/
28. Desmopressin/ad, ae, dt
29. (desmopressin* or vasopressin deamino or nocutil or octim or minurin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or ddavp or ddavp or adiuretin or octostim or desmogalen).tw.
30. *Thrombopoietin Receptor/
31. Eltrombopag/
32. Romiplostim/
33. (eltrombopag* or promacta* or revolade* or romiplastin* or romiplostim* or nplate*).tw.
34. (amg531 or amg 531 or amg-531 or sb497115 or sb 497115 or sb-497115 or fab59 or fab 59 or fab-59 or AKR501 or AKR 501 or AKR-501 or YM477 or YM 477 or YM-477 or Peg-TPOmp*).tw.
35. ((TPO or thrombopoietin) adj (mimetic* or receptor agonist* or agonist*)).tw.
36. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw.
37. or/18-36
38. 17 and 37

Appendix 5. CINAHL (EBSCOhost) search strategy

S1 (MH “Hematologic Neoplasms+”)

S2 (MH Leukemia+)

S3 (MH Lymphoma+)

S4 (MH “Multiple Myeloma+”)

S5 (MH “Anemia, Aplastic+”)

S6 (MH “Bone Marrow Diseases+”)

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S7 (MH Thrombocytopenia+)

S8 (thrombocytop* or leukemic* or leukaemia* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)

S9 ((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*))

S10 (MH “Antineoplastic Agents+”)

S11 (MH “Hematopoietic Stem Cell Transplantation”)

S12 (MH “Bone Marrow Transplantation”)

S13 (MH Radiotherapy+)

S14 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)

S15 ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) N2 patients)

S16 TI (malignan* or oncolog* or cancer*)

S17 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 OR S15 OR S16

S18 (MH “BLOOD COAGULATION FACTORS+”)

S19 (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or eptacog* or proconvertin or fibrinogen concentrate* or factor I OR haemocomplettan* OR octafibrin* OR riastap*)

S20 ((activated N2 factor seven) or (activated N2 factor vii) or (activated N3 rfvii) or (activated N2 fvii))

S21 TI (factor seven or factor vii or factor 7)

S22 ((platelet* or thrombocyte*) N5 (substitute* or artificial*))

S23 platelet-poor plasma*

S24 (MH Desmopressin)

S25 (desmopressin* or vasopressin deamino or nocutil or octim or minurin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or ddavp or ddavp or adiuretin or octostim or desmogalen)

S26 (MH “Benzoic Acids Therapeutic Use”)

S27 (MH “Receptors, Cell Surface Therapeutic Use”)

S28 (eltrombopag* or promacta* or revolade* or romiplastin* or romiplostim* or nplate*)

S29 (amg531 or amg 531 or amg-531 or sb497115 or sb 497115 or sb-497115 or fab59 or fab 59 or fab-59 or AKR501 or AKR 501 or AKR-501 or YM477 or YM 477 or YM-477 or Peg-TPOmp*)

S30 ((TPO or thrombopoietin) W1 (mimetic* or receptor agonist* or agonist* or agent*))

S31 (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) N5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) W1 factor*))

S32 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26OR S27 OR S28 OR S29 OR S30 OR S31

S33 S170 AND S32

Appendix 6. TRANSFUSION EVIDENCE LIBRARY search strategy

#1 HAEMATOLOGICAL MALIGNANCIES [Keywords]

#2 (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR multiple myeloma OR plasma cell myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR Hodgkin*)

#3 ((haematolog* OR hematolog* OR blood OR red cell* OR white cell* OR lymphom* OR marrow OR platelet*) AND (malignan* OR oncolog* OR cancer OR cancers OR neoplasm*))

#4 #1 OR #2 OR #3

#5 FACTOR VIIA [Keywords]

#6 (“factor viia” OR “factor 7a” OR rfviia OR fviia OR novoseven* OR “novo seven*” OR eptacog* OR proconvertin OR “fibrinogen concentrate*” OR “factor I” OR haemocomplettan* OR octafibrin* OR riastap* OR “activated factor seven” OR “activated factor vii” OR “activated rfvii” OR “activated fvii” OR “factor seven” OR “factor vii” OR “factor 7”) [In Title]

#7 ((platelet* OR thrombocyte*) AND (substitute* OR artificial*))

#8 (platelet-poor plasma* OR desmopressin* OR vasopressin deamino OR nocutil OR octim OR minurin OR deamino-8-d-arginine vasopressin OR vasopressin 1-desamino-8-arginine OR desmotabs OR ddavp OR ddavp OR adiuretin OR octostim OR desmogalen OR eltrombopag* OR promacta* OR revolade* OR romiplastin* OR romiplostim* OR nplate*)

#9 (amg531 OR amg 531 OR amg-531 OR sb497115 OR sb 497115 OR sb-497115 OR fab59 OR fab 59 OR fab-59 OR AKR501 OR AKR 501 OR AKR-501 OR YM477 OR YM 477 OR YM-477 OR Peg-TPOmp*)

#10 ((TPO OR thrombopoietin) AND (mimetic* OR agonist* OR agent*))

#11 ((haemosta* OR hemosta* OR antihaemorrhag* OR antihemorrhag* OR anti haemorrhag* OR anti-hemorrhag*) AND (drug OR drugs OR agent* OR treatment* OR therapy OR therapies))

#12 “coagulation factor” OR “clotting factor” OR “coagulation factors” OR “clotting factors”

#13 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 #4 AND #13

Appendix 7. Web of Science (CPCI-S) search strategy

((“factor viia” OR “factor 7a” OR rfviia OR fviia OR novoseven OR “novo seven” OR eptacog OR proconvertin OR “fibrinogen concentrate” OR “factor I” OR haemocomplettan OR octafibrin OR riastap OR “activated factor seven” OR “activated factor vii” OR “activated rfvii” OR “activated fvii” OR “factor seven” OR “factor vii” OR “factor 7” OR “platelet-poor plasma” OR desmopressin OR eltrombopag OR promacta OR revolade OR romiplastin OR romiplostim OR nplate OR “thrombopoietin receptor*” OR “thrombopoietin agonist*” OR “thrombopoietin mimetic*”) AND (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR Hodgkin* OR haematological OR hematological)) [in Title]

AND (randomized OR randomised OR randomly) [in Title]

Appendix 8. LILACS search strategy

((“factor viia” OR “factor 7a” OR rfviia OR fviia OR novoseven OR “novo seven” OR eptacog OR proconvertin OR “fibrinogen concentrate” OR “factor I” OR haemocomplettan OR octafibrin OR riastap OR “activated factor seven” OR “activated factor vii” OR “activated rfvii” OR “activated fvii” OR “factor seven” OR “factor vii” OR “factor 7” OR “platelet-poor plasma” OR desmopressin OR eltrombopag OR promacta OR revolade OR romiplastin OR romiplostim OR nplate OR “thrombopoietin receptor$” OR “thrombopoietin agonist$” OR “thrombopoietin mimetic$”) AND (thrombocytop$ OR leukemi$ OR leukaemi$ OR lymphoma$ OR aplastic anemia OR aplastic anaemia OR myelodysplas$ OR myeloproliferat$ OR myeloma OR thrombocythemi$ OR thrombocythaemi$ OR polycythemi$ OR polycythaemi$ OR myelofibros$ OR Hodgkin$ OR haematological OR hematological)) AND db:(“LILACS”) AND type_of_study:(“clinical_trials” OR “systematic_reviews”)

Appendix 9. INDMED search strategy

((factor viia OR factor 7$ OR rfvii$ OR fvii$ OR factor seven OR factor vii OR novoseven OR novo seven OR eptacog OR proconvertin OR fibrinogen OR factor I OR haemocomplettan OR octafibrin OR riastap OR platelet-poor plasma OR desmopressin OR eltrombopag OR promacta OR revolade OR romiplastin OR romiplostim OR nplate OR

thrombopoietin receptor$ OR thrombopoietin agonist$ OR thrombopoietin mimetic$) AND (thrombocytop$ OR leukemi$ OR leukaemi$ OR lymphoma$ OR aplastic OR myelodysplas $ OR myeloproliferat$ OR myeloma OR thrombocythemi$ OR thrombocythaemi$ OR polycyth$ OR myelofibros$ OR Hodgkin$ OR haematological OR hematological OR haematopoietic OR hematopoietic) AND (random$ OR blind$ OR trial$ OR control$))

Appendix 10. KOREAMED & PAKMEDINET search strategy

"factor viia"[ALL] AND "Randomized Controlled Trial" [PT]

novoseven[ALL] AND "Randomized Controlled Trial" [PT]

fibrinogen[ALL] AND "Randomized Controlled Trial" [PT]

haemocomplettan[ALL] AND "Randomized Controlled Trial" [PT]

octafibrin[ALL] AND "Randomized Controlled Trial" [PT]

riastap[ALL] AND "Randomized Controlled Trial" [PT]

"platelet-poor plasma" [ALL] AND "Randomized Controlled Trial" [PT]

desmopressin[ALL] AND "Randomized Controlled Trial" [PT]

eltrombopag[ALL] AND "Randomized Controlled Trial" [PT]

promacta[ALL] AND "Randomized Controlled Trial" [PT]

revolade[ALL] AND "Randomized Controlled Trial" [PT]

romiplostim[ALL] AND "Randomized Controlled Trial" [PT]

nplate[ALL] AND "Randomized Controlled Trial" [PT]

"thrombopoietin receptor agonist*"[ALL] "Randomized Controlled Trial" [PT]

Appendix 11. ClinicalTrials.gov & ICTRP search strategy

Search Terms/Title: randomized OR randomised

Conditions: hematological neoplasm OR hematological malignancies OR leukemia OR lymphoma OR thrombocytopenia OR multiple myeloma OR aplastic anemia OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkins disease

Intervention: factor viia OR rFVIIa OR recombinant factor vii OR activated factor vii OR desmopressin OR eptacog OR proconvertin OR fibrinogen concentrate OR haemocomplettan OR octafibrin OR riastap OR platelet-poor plasma OR eltrombopag OR promacta OR revolade OR romiplostim OR thrombopoietin receptor agonist

Appendix 12. ISRCTN search strategy

(hematological OR haematological OR leukemi% OR leukaemi% OR lymphoma OR thrombocytopenia% OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR

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myelofibrosis OR hodgkin%) AND (factor viia OR rFVIIa OR factor vii OR novoseven OR desmopressin) AND random%

(hematological OR haematological OR leukemi% OR leukaemi% OR lymphoma OR thrombocytopenia% OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin%) AND (eptacog OR proconvertin OR fibrinogen concentrate OR haemocomplettan) AND random%

(hematological OR haematological OR leukemi% OR leukaemi% OR lymphoma OR thrombocytopenia% OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin%) AND (octafibrin OR riastap OR platelet-poor plasma OR eltrombopag) AND random%

(hematological OR haematological OR leukemi% OR leukaemi% OR lymphoma OR thrombocytopenia% OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin%) AND (promacta OR revolade OR romiplostim OR nplate OR receptor agonist) AND random%

Appendix 13. EU Clinical Trials Register search strategy

(hematological OR haematological OR leukemi* OR leukaemi* OR lymphoma OR thrombocytopeni* OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin*) AND (novoseven OR rFVIIa OR desmopressin OR eptacog OR proconvertin* OR fibrinogen OR haemocomplettan* OR octafibrin* OR riastap* OR eltrombopag* OR promacta* OR revolade* OR romiplostim* OR nplate* OR thrombopoietin) AND random*

OR

factor viia AND random*

OR

recombinant factor vii AND random*

OR

platelet-poor plasma AND random*

Appendix 14. Hong Kong Clinical Trials Registry search strategy

Disease Group: Blood and blood-forming organs

Title: randomized OR randomised

DECLARATIONS OF INTEREST

Lise Estcourt: none declared.

Richard Gregg: none declared.

Simon Stanworth: none declared.

Carolyn Doree: none declared.

Marialena Trivella: none declared.

Sally Hopewell: none declared.

Mike Murphy: none declared.

Alan Tinmouth: none declared.

Additional references

** Indicates the major publication for the study*

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