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## **Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review (Review)**

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Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review (Review)

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**WILEY**

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# Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

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## ABSTRACT

### Background

People with thrombocytopenia due to bone marrow failure are vulnerable to bleeding. Platelet transfusions have limited efficacy in this setting and alternative agents that could replace, or reduce platelet transfusion, and are effective at reducing bleeding are needed.

### Objectives

To compare the relative efficacy of different interventions for patients with thrombocytopenia due to chronic bone marrow failure and to derive a hierarchy of potential alternative treatments to platelet transfusions.

### Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (the Cochrane Library 2016, Issue 3), MEDLINE (from 1946), Embase (from 1974), CINAHL (from 1937), the Transfusion Evidence Library (from 1980) and ongoing trial databases to 27 April 2016.

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## Selection criteria

We included randomised controlled trials in people with thrombocytopenia due to chronic bone marrow failure who were allocated to either an alternative to platelet transfusion (artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, recombinant activated factor VII (rFVIIa), desmopressin (DDAVP), recombinant factor XIII (rFXIII), recombinant interleukin (rIL)6 or rIL11, or thrombopoietin (TPO) mimetics) or a comparator (placebo, standard of care or platelet transfusion). We excluded people undergoing intensive chemotherapy or stem cell transfusion.

## Data collection and analysis

Two review authors independently screened search results, extracted data and assessed trial quality. We estimated summary risk ratios (RR) for dichotomous outcomes. We planned to use summary mean differences (MD) for continuous outcomes. All summary measures are presented with 95% confidence intervals (CI).

We could not perform a network meta-analysis because the included studies had important differences in the baseline severity of disease for the participants and in the number of participants undergoing chemotherapy. This raised important concerns about the plausibility of the transitivity assumption in the final dataset and we could not evaluate transitivity statistically because of the small number of trials per comparison. Therefore, we could only perform direct pairwise meta-analyses of included interventions.

We employed a random-effects model for all analyses. We assessed statistical heterogeneity using the  $I^2$  statistic and its 95% CI. The risk of bias of each study included was assessed using the Cochrane 'Risk of bias' tool. The quality of the evidence was assessed using GRADE methods.

## Main results

We identified seven completed trials (472 participants), and four ongoing trials (recruiting 837 participants) which are due to be completed by December 2020. Of the seven completed trials, five trials (456 participants) compared a TPO mimetic versus placebo (four romiplostim trials, and one eltrombopag trial), one trial (eight participants) compared DDAVP with placebo and one trial (eight participants) compared tranexamic acid with placebo. In the DDAVP trial, the only outcome reported was the bleeding time. In the tranexamic acid trial there were methodological flaws and bleeding definitions were subject to significant bias. Consequently, these trials could not be incorporated into the quantitative synthesis. No randomised trial of artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, rFVIIa, rFXIII, rIL6 or rIL11 was identified.

We assessed all five trials of TPO mimetics included in this review to be at high risk of bias because the trials were funded by the manufacturers of the TPO mimetics and the authors had financial stakes in the sponsoring companies.

The GRADE quality of the evidence was very low to moderate across the different outcomes.

There was insufficient evidence to detect a difference in the number of participants with at least one bleeding episode between TPO mimetics and placebo (RR 0.86, 95% CI 0.56 to 1.31, four trials, 206 participants, *low-quality evidence*).

There was insufficient evidence to detect a difference in the risk of a life-threatening bleed between those treated with a TPO mimetic and placebo (RR 0.31, 95% CI 0.04 to 2.26, one trial, 39 participants, *low-quality evidence*).

There was insufficient evidence to detect a difference in the risk of all-cause mortality between those treated with a TPO mimetic and placebo (RR 0.74, 95%CI 0.52 to 1.05, five trials, 456 participants, *very low-quality evidence*).

There was a significant reduction in the number of participants receiving any platelet transfusion between those treated with TPO mimetics and placebo (RR 0.76, 95% CI 0.61 to 0.95, four trials, 206 participants, *moderate-quality evidence*).

There was no evidence for a difference in the incidence of transfusion reactions between those treated with TPO mimetics and placebo (pOR 0.06, 95% CI 0.00 to 3.44, one trial, 98 participants, *very low-quality evidence*).

There was no evidence for a difference in thromboembolic events between TPO mimetics and placebo (RR 1.41, 95%CI 0.39 to 5.01, five trials, 456 participants, *very-low quality evidence*).

There was no evidence for a difference in drug reactions between TPO mimetics and placebo (RR 1.12, 95% CI 0.83 to 1.51, five trials, 455 participants, *low-quality evidence*).

No trial reported the number of days of bleeding per participant, platelet transfusion episodes, mean red cell transfusions per participant, red cell transfusion episodes, transfusion-transmitted infections, formation of antiplatelet antibodies or platelet refractoriness.

In order to demonstrate a reduction in bleeding events from 26 in 100 to 16 in 100 participants, a study would need to recruit 514 participants (80% power, 5% significance).

### Authors' conclusions

There is insufficient evidence at present for thrombopoietin (TPO) mimetics for the prevention of bleeding for people with thrombocytopenia due to chronic bone marrow failure. There is no randomised controlled trial evidence for artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, rFVIIa, rFXIII or rIL6 or rIL11, antifibrinolytics or DDAVP in this setting.

## PLAIN LANGUAGE SUMMARY

### Alternative agents instead of platelet transfusions to prevent bleeding for people who have bone marrow disorders and low platelet counts

#### Review question

We evaluated the evidence about whether giving agents that can replace, or reduce platelet transfusion (artificial platelets, platelet-poor plasma, fibrinogen concentrate, recombinant activated factor VII (rFVIIa), recombinant factor XIII (rFXIII), recombinant interleukin (rIL)6 or rIL11, desmopressin (DDAVP), thrombopoietin (TPO) mimetics or antifibrinolytic drugs), to people with a low platelet count prevents bleeding and whether these alternative agents are associated with side effects. Our target population was people with bone marrow disorders which prevent them from producing enough platelets. We excluded people undergoing intensive chemotherapy or stem cell transplantation.

#### Background

People with low platelet counts due to bone marrow disorders are vulnerable to bleeding which may be severe or life-threatening. In order to treat, or prevent bleeding, they are often given platelet transfusions. However, platelet transfusions are associated with risks such as infection and transfusion reactions. Consequently, there is interest in whether it is possible to use alternative treatments to prevent bleeding. These treatments include: man-made platelets (artificial platelets); stimulating the person's body to produce more platelets (recombinant interleukin (rIL)6, rIL11, TPO mimetics); increasing the levels of proteins in the blood that help the body to form a clot (platelet-poor plasma, fibrinogen concentrate, recombinant activated factor VII (rFVIIa), recombinant factor XIII (rFXIII)); and preventing a blood clot from breaking down (antifibrinolytics). There may be risks associated with agents that prevent bleeding; the most important being an increased risk of forming unwanted blood clots, which could be potentially life-threatening.

#### Study characteristics

The evidence is current to April 2016. We identified 11 randomised controlled trials, of which seven had been completed. Of the seven completed trials, five trials (456 participants) assessed TPO mimetics, one trial (eight participants) assessed tranexamic acid and one trial (eight participants) assessed DDAVP. The trial of DDAVP only assessed the bleeding time: the time taken for bleeding to stop after a small cut is made in the participant's forearm. It did not assess any of the outcomes of interest to this review. The trial of tranexamic acid had significant methodological flaws in the way bleeding was reported. No randomised trial of artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, rFVIIa, rFXIII, rIL6 or rIL11 was identified. Consequently, quantitative analysis was only performed on the five trials assessing TPO mimetics. Four of these trials included adults with myelodysplastic syndrome (MDS) and one trial assessed adults with MDS or acute myeloid leukaemia (AML). We assessed all five trials of TPO mimetics included in this review to be at high risk as the manufacturers if the TPO mimetics were directly involved in the design and publication of the trials.

Differences in severity of disease and number of participants undergoing chemotherapy between trials meant that network meta-analysis could not be performed. A requirement of network meta-analysis is that participants in each trial should meet the eligibility criteria for each trial that is included.

The four ongoing trials are all comparing TPO mimetics versus placebo; they are expected to recruit 837 participants in total and are due to be completed by December 2020.

#### Key results

TPO mimetics may make little or no difference to the number of participants with any bleeding or severe/life-threatening bleeding. We are very uncertain whether TPO mimetics reduce the risk of mortality. TPO mimetics probably reduce the number of participants

who need a platelet transfusion. We are very uncertain whether TPO mimetics reduce the risk of transfusion reactions or risk of thromboembolism. TPO mimetics may have little or no effect on the risk of drug reactions.

No trial reported the number of days bleeding per participant, platelet transfusion episodes, mean red cell transfusions per participant, red cell transfusion episodes, transfusion-transmitted infections, formation of antiplatelet antibodies or platelet refractoriness.

### **Quality of the evidence**

The quality of the evidence was low or very low for all outcomes except the number of participants receiving a platelet transfusion which was moderate-quality evidence.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient or population: People with chronic bone marrow failure Intervention: Thrombopoietin mimetics Comparison: Placebo					
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Thrombopoietin mimetic			
Number of participants with at least one bleeding episode	Study population		RR 0.86 (0.56 to 1.31)	206 (4 RCTs)	⊕⊕○○ LOW <sup>12</sup>
	315 per 1000	271 per 1000 (176 to 413)			
Number of participants with at least one severe or life-threatening bleeding episode	Study population		RR 0.31 (0.04 to 2.26)	40 (1 RCT)	⊕⊕○○ LOW <sup>12</sup>
	154 per 1000	48 per 1000 (6 to 348)			
All-cause mortality	Study population		RR 0.74 (0.52 to 1.05)	456 (5 RCTs)	⊕○○○ VERY LOW <sup>13</sup>
	237 per 1000	176 per 1000 (123 to 249)			
Proportion of participants receiving a platelet transfusion	Study population		RR 0.76 (0.61 to 0.95)	206 (4 RCTs)	⊕⊕⊕○ MODERATE <sup>1</sup>
	658 per 1000	500 per 1000 (401 to 625)			
Transfusion reactions	Study population		pOR 0.06 (0.00 to 3.44)	98 (1 RCT)	⊕○○○ VERY LOW <sup>134</sup>

	29 per 1000	2 per 1000 (0 to 94)			
Thromboembolism	Study population		RR 1.41 (0.39 to 5.01)	456 (5 RCTs)	⊕○○○ VERY LOW <sup>13</sup>
	19 per 1000	27 per 1000 (8 to 97)			
Drug reactions	Study population		RR 1.12 (0.83 to 1.51)	455 (5 RCTs)	⊕⊕○○ LOW <sup>12</sup>
	271 per 1000	303 per 1000 (225 to 409)			
Number of red cell transfusions per participant	Meta-analysis not possible		Not estimable	98 (1 RCT)	-  Participants treated with eltrombopag received mean 4.8 units red blood cells whereas those treated with placebo received mean 6.3 units over 6 months

\* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; pOR: Peto Odds ratio;

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> Downgraded one point due to risk of bias

<sup>2</sup> Downgraded one point due to imprecision

<sup>3</sup> Downgraded two points due to low event rate

<sup>4</sup> Downgraded one point due to indirectness



## BACKGROUND

### Description of the condition

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

Clinical symptoms of people with bone marrow failure disorders are related to cytopenia, that is, the failure to produce adequate numbers of normal red cells, white cells, or platelets. People can present with fatigue and shortness of breath due to anaemia, recurrent infections due to neutropenia (reduced numbers of white cells - neutrophils), and bleeding or bruising due to thrombocytopenia (reduced numbers of platelets). Bleeding is a result of a failure to produce adequate numbers of platelets because of insufficient numbers of bone marrow megakaryocytes (cells in the bone marrow that produce platelets) or megakaryocyte dysfunction. Bone marrow failure disorders can also be associated with an increased risk of progression to acute leukaemia.

Bone marrow failure disorders can be classified according to the underlying pathophysiology, into four broad categories: myelodysplastic syndromes (MDS), primary myelofibrosis, acquired aplastic anaemia, and inherited bone marrow failure disorders.

MDS encompasses a diverse group of disorders that are characterised by dysplasia in one or more cell lines (blood cells have an abnormal shape or size), ineffective haematopoiesis, and an increased risk of developing acute myeloid leukaemia (AML). Overall, the incidence of MDS is estimated at between 2.3 to 4.5 per 100,000 per year; however, incidence increases markedly with age, peaking in those aged over 80 years (> 30 per 100,000 per year) (Dinmohamed 2014; Ma 2007; Ma 2012; Neukirchen 2011). Several cohort studies have evaluated the incidence of thrombocytopenia at diagnosis (platelet count < 100 x 10<sup>9</sup>/L), which affects 23% to 93% of people with newly diagnosed MDS, depending on the cohort (Kantarjian 2007). Cohort studies report that haemorrhage is the cause of death in 14% to 24% cases of MDS (Foucar 1985; Gupta 1999; Kantarjian 2007; Konstantopoulos 1989; Lidbeck 1980).

Primary myelofibrosis is a clonal myeloproliferative disease whereby the normal bone marrow is replaced by fibrosis, resulting in bone marrow failure. It has an incidence of 2.2 to 9.9 per million per year (Titmarsh 2014). People may develop a number of symptoms including fatigue, sweats, fevers, weight loss and an enlarged spleen, as well as symptoms of bone marrow failure (Tefferi 2013).

Acquired aplastic anaemia is a disease that results in a hypocellular bone marrow with quantitative defects of all three cell lines. The incidence in Europe and North America is two per million population per year and has a biphasic age distribution with increasing

numbers of cases in those aged 10 to 25 years and those over 60 years (Heimpel 2000; Issaragrisil 2006; Montané 2008). The incidence in Asia is higher, with estimates ranging from 3.9 to 7.4 per million per year (Young 2008). The underlying cause of aplastic anaemia is unknown in most cases, but different reports have associated it with certain industrial chemicals (Young 2008), agricultural pesticides (Issaragrisil 2006; Muir 2003), drugs (Issaragrisil 2006; Young 2008), and hepatitis viruses (Rauff 2011).

Inherited bone marrow failure disorders that result in thrombocytopenia include those associated with a global haematopoietic defect such as Fanconi anaemia, Dyskeratosis congenita, or Swachman-Diamond syndrome, as well as disorders associated with isolated thrombocytopenia, such as thrombocytopenia with absent radii (TAR) and amegakaryocytic thrombocytopenia (Alter 2007). The most common inherited bone marrow disorder is Fanconi anaemia, which has a reported incidence of approximately 1 in 360,000 live births, with a carrier frequency of 1 in 300 (Swift 1971).

Treatment is tailored to the needs of individual people but may include intensive treatment with allogeneic stem cell transplantation (Dokal 2008). Other people are managed symptomatically, with low-dose chemotherapy, or in the case of aplastic anaemia, with immunosuppressive agents, with a focus on maintaining quality of life, prolonging life and delaying transformation to acute leukaemia.

### Description of the intervention

Platelet transfusions are of some benefit in managing active bleeding for people with bone marrow failure and severe thrombocytopenia. The standard practice in most haematology units across the developed world is to use prophylactic transfusions in line with guidelines (BCSH 2003; BCSH 2004; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007). For chronic bone marrow failure, prophylactic platelet transfusions are standard for people with a platelet count less than 10 x 10<sup>9</sup>/L and a haemorrhagic phenotype, but for people without a haemorrhagic phenotype, platelet transfusions are not given. It is still uncertain how best to use platelet transfusions to prevent severe and life-threatening bleeding (Estcourt 2011). Alternative agents which could replace or reduce platelet transfusions may be more effective than platelet transfusions at controlling bleeding and will have a different side-effect profile. Alternatives include artificial platelet substitutes, platelet-poor plasma, recombinant factor VIIa (rFVIIa), fibrinogen, recombinant factor XIII (rFXIII), thrombopoietin (TPO) mimetics and antifibrinolytic drugs.

### How the intervention might work

In normal haemostasis (formation of a blood clot), platelets form a primary haemostatic plug that is consolidated by the deposi-

tion of cross-linked fibrin. Platelet adhesion depends on normal platelet function, the presence of von Willebrand factor, and extracellular matrix components such as collagen and fibronectin (Ruggeri 2007). When the platelet count is low, the standard treatment has been to transfuse platelets, although this procedure can be associated with hazards such as infection, transfusion reactions and formation of anti-platelet antibodies. Additionally, 18% to 23% people with bone marrow failure due to MDS have a haemorrhagic phenotype regardless of their platelet count (Kantarjian 2007). Alternatives to platelet transfusion aim to either simulate the effects of platelets (artificial platelet substitutes), stimulate additional fibrin formation (platelet-poor plasma, recombinant factor VIIa and fibrinogen), promote von Willebrand factor release and platelet function (desmopressin), or increase platelet production (TPO mimetics). These agents aim to promote haemostasis without the side effects associated with platelet transfusions. The important adverse event for any pro-haemostatic intervention is thrombosis, and any of these interventions have the potential to cause it. Other specific adverse events are listed below with the description of the intervention.

### Artificial platelet substitutes

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

### Platelet-poor plasma (PPP)

Platelet-poor plasma (PPP) is a source of clotting factors and fibrinogen and can be administered intravenously. PPP is a blood component and is associated with a small risk of transfusion reactions and transfusion-transmitted infections (Desborough 2012).

### Recombinant factor VIIa (rFVIIa)

Recombinant factor VIIa (rFVIIa) is an intravenous drug licensed for people with haemophilia and inhibitory allo-antibodies, and for prophylaxis and treatment of people with congenital factor VII deficiency. It is used off-license in a number of other settings, including operations where blood loss cannot be controlled by other means. However, the effectiveness of its use in people without haemophilia is unproven. This is an expensive agent compared to platelet transfusion and repeated doses every two to three hours are often necessary (Joint Formulary Committee 2016). It has an advantage of not being a biological agent (Simpson 2012).

### Fibrinogen concentrate

The final step of the coagulation cascade is the formation of a fibrin clot. The substrate for fibrin is fibrinogen, which is converted into fibrin by the action of thrombin. Fibrinogen concentrate is administered intravenously and may result in some reduction in surgical bleeding when administered pre-operatively, although the overall quality of evidence for this is low (Wikkelsø 2013). Fibrinogen concentrate is a blood component and is associated with a theoretical risk of viral infection. However, viral inactivation is involved in its manufacture and is likely to make this risk very low (Franchini 2012).

### Recombinant factor XIII (rFXIII)

In a normal clot, when single strands of fibrin have been formed, they are cross-linked by factor XIII, giving the clot strength. Trials of rFXIII have taken place in people undergoing cardiac surgery to assess whether this reduced postsurgical bleeding (Karkouti 2013).

### Desmopressin (DDAVP)

Desmopressin (DDAVP) is a vasopressin analogue that increases the plasma levels of factor VIII (FVIII) and von Willebrand factor (vWF) two- to three-fold. It is used to treat people with mild haemophilia A or von Willebrand disease and has also been used to treat people with uraemia, liver cirrhosis, congenital platelet function disorders and drug-induced platelet dysfunction (Svensson 2014). It can be administered intravenously, subcutaneously or intranasally. These different routes of administration result in different levels of vWF and factor VIII response (Mannucci 1987). If we include trials comparing more than one route of administration of DDAVP, then we will perform sensitivity analyses to determine if they can be combined as a single node. DDAVP is a well-tolerated medication, but it is associated with facial flushing and can potentially cause hyponatraemic seizures in people who are not fluid-restricted (Svensson 2014). It has a short duration of action and is more likely to be used for prophylaxis prior to procedures than for long-term prophylaxis. It is not a biological product and is less expensive than platelet transfusion (Joint Formulary Committee 2016).

### Thrombopoietin (TPO) mimetics

The liver synthesises thrombopoietin (TPO), which is the key regulator of bone marrow platelet production. TPO mimetics have been used in several disease states to promote both megakaryopoiesis and thrombopoiesis (Kuter 2014). The two main TPO mimetics in current use are romiplostim (weekly injection) and eltrombopag (daily oral tablet), both of which are recommended by the National Institute for Health and Care Excellence (NICE) for use in adults with immune thrombocytopenia (ITP) who have severe disease and a high risk of bleeding (NICE 2011; NICE 2013). While a systematic review found that these agents improve

platelet counts, there was no evidence that TPO receptor agonists reduced the risk of significant bleeding for people with ITP (Zeng 2011). TPO mimetics are more expensive than platelet transfusions (Joint Formulary Committee 2016). Interleukin 6 and interleukin 11 may also act as stimulants of thrombopoiesis (Gordon 1995; Kurzrock 2001; Tsimberidou 2005). Recombinant interleukin 6 and 11 are not in routine clinical use, so their costs are unclear at present.

### Antifibrinolytic drugs

Fibrinolysis is the process by which blood clots are broken down after they have been formed. Anti-fibrinolytic drugs block this process, resulting in greater clot strength. The three most commonly used antifibrinolytic drugs are tranexamic acid, aprotinin and epsilon-aminocaproic acid. A previous Cochrane systematic review assessed these agents (Estcourt 2016), which are included in this review for comparison with other potential interventions as part of our planned network meta-analysis. Antifibrinolytics are cheaper than platelet transfusions (Joint Formulary Committee 2016).

### Why it is important to do this review

This review is focused on whether alternative agents to prophylactic platelet transfusions are effective for the prevention and control of life-threatening thrombocytopenic bleeding. Platelet transfusions are expensive and may lead to adverse events such as infections and platelet refractoriness, particularly in groups of people who receive multiple transfusions, such as those with chronic bone marrow failure. Some people with bone marrow failure bleed despite apparently adequate platelet numbers, and alternative methods for managing bleeding will be necessary. This review is also important for the developing world, where access to safe blood components is much more limited (Verma 2009).

## OBJECTIVES

To compare the relative efficacy of different treatments for thrombocytopenia (artificial platelet substitutes, platelet-poor plasma, fibrinogen, rFVIIa, rFXIII, thrombopoietin mimetics, antifibrinolytic drugs or platelet transfusions) in people with chronic bone marrow failure and to derive a hierarchy of potential alternate treatments to platelet transfusions.

## METHODS

### Criteria for considering studies for this review

### Types of studies

Only randomised controlled trials (RCTs) were included.

### Types of participants

We included inpatients and outpatients of all ages with thrombocytopenia due to chronic bone marrow failure. Only data from the bone marrow failure subgroups were used for trials consisting of mixed populations of participants (e.g. those with diagnoses of immune thrombocytopenic purpura). If subgroup data for participants with bone marrow failure were not available (even after contacting the authors of the trial), we excluded the trial if fewer than 80% of participants had bone marrow failure. We excluded any participants who did not have thrombocytopenia due to bone marrow failure, as well as participants undergoing intensive chemotherapy or stem cell transplantation, as this is the focus of another Cochrane review (Desborough 2016b). We included participants with bone marrow failure syndromes (e.g. aplastic anaemia, congenital bone marrow failure syndromes, MDS and myelofibrosis) who were not being treated with intensive chemotherapy or an allogeneic stem cell transplant.

### Types of interventions

We considered the following interventions (alternative agents that could replace or reduce platelet transfusion) without restrictions on the dose compared to each other or to placebo.

- Artificial platelet substitutes.
- Platelet-poor plasma.
- Recombinant factor VIIa (rFVIIa).
- Fibrinogen.
- Recombinant factor XIII (rFXIII).
- TPO mimetics (we analysed the most commonly used TPO mimetics, eltrombopag and romiplostim, separately and in combination).
  - Interleukin 6 or interleukin 11.
  - Desmopressin.
  - Anti-fibrinolytics (such as tranexamic acid).

We included randomised controlled trials (RCTs) that evaluated one or more of the interventions listed above. We report the findings for all interventions in the results and conclusions of the review.

### Types of outcome measures

We categorised all outcomes according to short-, medium-, and long-term outcomes. Studies that met the other inclusion criteria were included in this review regardless of whether they included these outcomes. We reported the exact definition of these time frames over time periods that were common to as many studies as possible (e.g. up to 30 days, one to six months, and greater than six months from day of randomisation). We planned to use the

primary outcomes and adverse events to develop a hierarchy of treatments.

### Primary outcomes

- Number of participants with at least one bleeding episode
- Number of participants with at least one severe or life-threatening bleeding episode
- Number of days bleeding occurred per participant

### Secondary outcomes

- Mortality
  - Overall mortality
  - Mortality due to bleeding
  - Mortality due to infection
- Platelet transfusions
  - Proportion of participants requiring a platelet transfusion
  - Number of units of platelets transfused per participant
  - Mean number of platelet transfusion episodes per participant
- Red cell transfusions
  - Proportion of participants requiring a red cell transfusion
  - Number of units of red cells transfused per participant
  - Number of red cell transfusion episodes per participant
- Adverse events (e.g. transfusion reactions, transfusion-transmitted infections, thromboembolism, development of platelet antibodies, development of platelet refractoriness, drug reactions)

## Search methods for identification of studies

The Systematic Review Initiative (SRI) Information Specialist (CD) formulated the search strategies in collaboration with the Cochrane Haematological Malignancies Group. The search included all possible comparisons formed by the interventions of interest.

### Electronic searches

#### Bibliographic databases

We searched for randomised controlled trials in the following databases.

- CENTRAL, DARE, HTA & NHSEED (the Cochrane Library 2016, Issue 3) ([Appendix 1](#))
- MEDLINE (1946 to 27 April 2016) ([Appendix 2](#))
- Embase (1974 to 27 April 2016) ([Appendix 3](#))
- CINAHL (1937 to 27 April 2016) ([Appendix 4](#))
- PUBMED (epublications only) ([Appendix 5](#))

- TRANSFUSION EVIDENCE LIBRARY (1980 to 27 April 2016) ([Appendix 6](#))
- LILACS (1982 to 27 April 2016) ([Appendix 7](#))
- IndMed (1986 to 27 April 2016) ([Appendix 8](#))
- KoreaMed (1997 to 27 April 2016) ([Appendix 9](#))
- Web of Science (Conference Proceedings Citation Index-Science (CPCI-S) - 1990 to 27 April 2016) ([Appendix 10](#))

We combined searches in MEDLINE, Embase and CINAHL with adaptations of the Cochrane RCT search filters, as described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)). We combined searches in CINAHL with the relevant SIGN RCT studies filter ([www.sign.ac.uk/methodology/filters.html](http://www.sign.ac.uk/methodology/filters.html)). We presented all search strategies in the appendices as indicated. There were no restrictions on language or publication status.

### Ongoing studies:

We identified ongoing trials with searches of ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/search>) ([Appendix 11](#)), the WHO International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) ([Appendix 12](#)) and the Hong Kong Clinical Trials Registry (<http://www.hkclinicaltrials.com/>) ([Appendix 13](#)) to 27 April 2016.

### Searching other resources

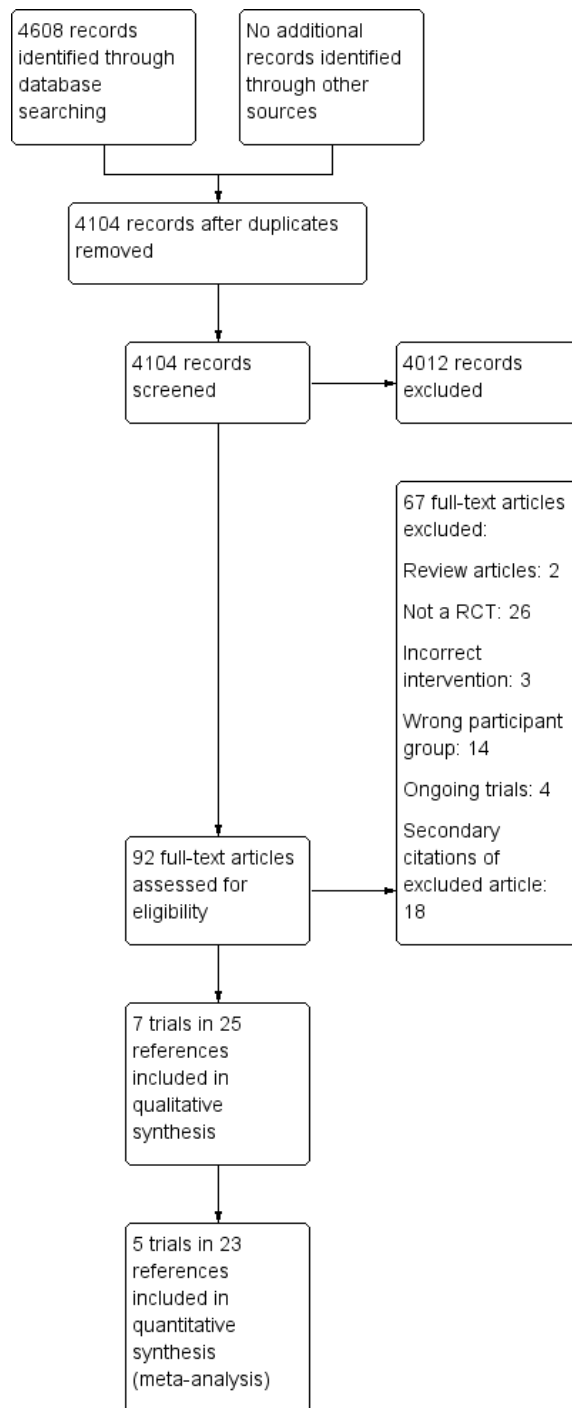
We handsearched references of all included trials, relevant review articles, and current treatment guidelines for further literature, limiting these searches to the 'first generation' reference lists.

## Data collection and analysis

### Selection of studies

We selected studies according to the methods described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). Two review authors (MD, AH) working independently initially screened all electronically derived citations and abstracts of papers identified by the review search strategy for relevance. Clearly irrelevant studies were excluded at this stage. The same two review authors then independently assessed the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We designed a study eligibility form to assess the relevance of trials on platelet transfusion, which helped ascertain whether the participants had thrombocytopenia due to bone marrow failure and whether trial arms differed according to their use of an alternative agent to prophylactic platelet transfusions. We recorded the reasons why potentially relevant studies failed to meet the eligibility criteria and displayed the results of the search in a PRISMA flow chart ([Hutton 2015](#)) ([Figure 1](#)).

**Figure 1. Study flow diagram.**



## Data extraction and management

Two review authors (MD, AH) conducted data extraction according to the guidelines proposed by Cochrane (Higgins 2011a). Disagreements between the review authors were resolved by consensus without the need for a third review author. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the trials. A related review team had previously piloted the data extraction forms (Desborough 2016b). The two authors (MD, AH) independently extracted the following data for all the studies.

- **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 and 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, sex, ethnicity, total number recruited, total number randomised, total number analysed, types of bone marrow failure, severity of disease, baseline platelet count, numbers lost to follow-up, dropouts (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment and prognostic factors. We used the type of bone marrow failure, severity of disease and baseline platelet count for the evaluation of the transitivity assumption (Jansen 2013; Salanti 2012).
- **Characteristics of interventions:** number of study arms, description of experimental arm(s), description of control arm, type of platelet transfusion given, timing of intervention, dosage of platelet given, compliance to interventions, additional interventions given especially in relation to red cell transfusions and any other differences between interventions.
- **Outcomes:** number and severity of bleeding episodes, mortality (all causes), mortality due to bleeding, mortality due to infection, mean number of platelet and red cell transfusions, proportion of participants requiring each type of transfusion and adverse events (e.g. transfusion reactions, transfusion-transmitted infections, thromboembolism, development of platelet antibodies, development of platelet refractoriness, drug reactions). We used both full-text versions and abstracts to retrieve data. We extracted arm-level data rather than study-level data. One review author (MD) entered data into software, and another (AH) checked the data entry for accuracy.
- **Data on potential effect modifiers:** For each individual study, we extracted data on the following study, intervention and

population characteristics that may have acted as effect modifiers.

- Cause of bone marrow failure.
- Severity of disease.
- Baseline platelet count.
- Concurrent medications.

## Assessment of risk of bias in included studies

We assessed the quality of all RCTs using the Cochrane 'Risk of bias' criteria, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (MD, AH) worked independently to assess each element of potential bias listed below as carrying a high, low or unclear risk. We describe the judgement statements upon which review authors have assessed potential bias in the [Characteristics of included studies](#) table. We reached consensus on the degree of risk of bias by comparing the review authors' statements. We used the 'Risk of bias' assessment to explore statistical heterogeneity in each included study. We used Cochrane's tool for assessing risk of bias (low, high or unclear risk) in the following areas.

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

We assessed risk of bias separately for each key outcome of the review.

## Measures of treatment effect

We recorded the number of events and the total number of participants in both the treatment and control groups for dichotomous outcomes (number of participants with at least one bleeding episode, number of participants with at least one severe or life-threatening bleeding episode, overall mortality, mortality due to bleeding, mortality due to infection, proportion of participants requiring a platelet transfusion, proportion of participants requiring a red cell transfusion, adverse events).

If data were available, we planned to record the mean, standard deviation and total number of participants in both the treatment and control groups for continuous outcomes (number of days bleeding occurred per participant, number of units of platelets transfused per participant, mean number of platelet transfusion episodes per participant, number of units of red cells transfused per participant, number of red cell transfusion episodes per participant). For studies providing only study-level data, we would have extracted the reported effect size with the corresponding standard error.



We planned to analyse continuous outcomes measured using the same scale, using the mean difference (MD) with 95% confidence intervals (CIs).

### Relative treatment effects

We reported risk ratios (RRs) with a 95% CI for dichotomous outcomes. When we could not report the available data in any of the formats described above, we provided a descriptive summary of the available information.

We estimated the pairwise relative treatment effects of the competing interventions using the proportion of participants with significant bleeding, the proportion of participants with an adverse events and the proportion of participants requiring a platelet transfusion. We then analysed these dichotomous outcomes by calculating a RR.

### Relative treatment ranking

We also considered the use of the surface area under the cumulative ranking curve (SUCRA) to obtain a hierarchy of the competing interventions for the primary outcomes and the adverse events (Salanti 2011).

### Unit of analysis issues

We dealt with unit of analysis issues according to the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

### Cross-over trials

Our search strategy identified two cross-over trials, but we were unable to use any data from these trials. If relevant cross-over trials are identified in future updates of this review, we will not assess the long-term outcomes mortality and proportion of participants in complete remission. We will assess other outcomes if the timing of the outcome measure occurred before the cross-over and if outcomes after the cross-over are not biased by the treatment before the cross-over. We will examine each trial individually to determine this eventuality.

### Cluster-randomised trials

We did not find any relevant cluster randomised trials, but for future updates of this review we plan to analyse cluster-randomised trials at the individual participant level, accounting for the cluster design and seek statistical advice.

### Studies with multiple treatment groups

We treated studies with multiple treatment groups as different independent two-arm studies. Where appropriate, the control group was split between the two intervention groups according to the guidelines in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). In the network meta-analysis the correlation included in the relative effects from multi-arm studies can be modelled properly.

### Dealing with missing data

We dealt with missing data according to the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We contacted authors in order to obtain information that was missing or unclear in the published report. In trials that included thrombocytopenic participants with bone marrow failure as well as participants with other causes of thrombocytopenia, we extracted data for the bone marrow failure subgroup from the general trial data. We recorded the number of participants lost to follow-up for each trial. We analysed data according to the intention-to-treat (ITT) principle, but if insufficient data were available, we planned to present per protocol (PP) analyses (Higgins 2011c). We also considered to perform a sensitivity analysis to evaluate the robustness of results when we move away from the available-case analysis using the informative missingness parameter framework (Mavridis 2014; White 2008).

### Assessment of heterogeneity

#### Assessment of clinical and methodological heterogeneity within treatment comparisons

When we considered the clinical and methodological characteristics of individual studies to be sufficiently homogenous, we combined the data to perform a meta-analysis (Deeks 2011). We did not report the overall summary statistic if excessive heterogeneity was present.

#### Assumptions when estimating the heterogeneity

We estimated different heterogeneity variances for each pairwise comparison. For the network meta-analysis, we would have considered a common heterogeneity parameter for each outcome.

#### Measures and tests for heterogeneity

We assessed statistical heterogeneity within each pairwise comparison using the  $I^2$  statistic and its 95% CI, which measured the percentage of variability that could not be attributed to random error ( $I^2 > 50\%$  moderate heterogeneity,  $I^2 > 80\%$  considerable heterogeneity). For the network meta-analysis, the assessment of

heterogeneity would be based on the magnitude of the on the magnitude of the heterogeneity variance parameter ( $\tau^2$ ) and its comparison with previously suggested empirical distributions (Rhodes 2015; Turner 2012). We would also estimate a total  $I^2$  value for heterogeneity in the network (Jackson 2014).

### Assessment of transitivity across treatment groups

We assessed whether the transitivity assumption is likely to hold by comparing epidemiologically and statistically, when possible, the clinical and methodological characteristics of the studies grouped by comparison (Jansen 2013; Salanti 2012). We considered that transitivity would be violated by differences across comparisons in the severity of disease, baseline platelet count and co-interventions such as chemotherapy.

### Assessment of reporting biases

We planned to explore the presence of small-study effects in direct meta-analyses by generating a funnel plot and statistically using a linear regression test if sufficient studies had been available. We considered a P value of less than 0.10 significant for this test (Sterne 2011). We also had planned to use contour-enhanced funnel plots to assess whether publication bias is likely to operate (Peters 2008), as well as comparison-adjusted funnel plots and network meta-regression models to assess the presence of small-study effects in the entire network (Chaimani 2012; Chaimani 2013).

## Data synthesis

### Direct meta-analysis

We performed direct meta-analyses according to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using aggregated data for analyses (Deeks 2011). Where there were sufficient data with enough similarities (in participants, interventions, settings and outcome measurement) between the data, we undertook meta-analyses using the Review Manager 5 software (RevMan 2014). One review author (MD) entered the data into the software, and a second (AH) checked it for accuracy. We used the random-effects model to pool the data when meta-analysis was feasible. We used the Mantel-Haenszel method for dichotomous outcomes and planned to use the inverse variance method for continuous outcomes. We planned to use the random-effect model for sensitivity analysis.

### Network meta-analyses

We could not perform a network meta-analysis because the included studies had important differences in the baseline severity of disease for the participants and in the number of participants undergoing chemotherapy. This raised important concerns about

the plausibility of the transitivity assumption in the final dataset and we could not evaluate transitivity statistically because of the small number of trials per comparison. Therefore, we could only perform direct pairwise meta-analyses of included interventions. For future updates of this review, we will perform network meta-analysis in Stata (StataCorp 2011) using the method of multivariate meta-analysis that treats the different comparisons in studies as different outcomes (White 2012).

### Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analyses and network meta-regression for each of the following variables in order to explain heterogeneity and/or inconsistency if sufficient studies had been available.

- Type of bone marrow failure disorder (MDS, aplastic anaemia, myelofibrosis or congenital bone marrow failure disorder)
- Severity of disease
- Baseline platelet count
- Study precision

### Sensitivity analysis

We assessed the robustness of the overall results by performing the following sensitivity analyses where appropriate with respect to those trials deemed to be at high risk of bias. For dichotomous data, we assessed the influence of participant dropout, analysing separately RCTs with less than 20% dropout, RCTs with 20% to 50% dropout and RCTs with greater than 50% dropout. We used the random-effects model for sensitivity analyses as part of the exploration of heterogeneity.

### 'Summary of findings' table

We used an approach that extends the GRADE system into network meta-analysis to build a 'Summary of findings' table, as suggested in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Salanti 2014; Schünemann 2011). We included the following outcomes for each type of comparison listed below.

- Number of participants with at least one bleeding episode.
- Number of participants with life-threatening or fatal bleeding.
- Number of platelet transfusions per participant.
- Number of red cell transfusions per participant.
- Adverse events - thromboembolism.
- Adverse events - transfusion or drug reactions.

## RESULTS



## Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of ongoing studies](#).

## Results of the search

The database searches identified 4608 references which were reduced to 4104 after duplicates were removed. These references were screened by two review authors (MD, AH) according to the criteria defined above, and we excluded 4012 references as either not an RCT or clearly outside the scope of this review (See PRISMA diagram [Figure 1](#)). The full text of the remaining 92 references were obtained. Sixty-seven were excluded (two review articles, 26 not RCTs, three incorrect intervention, 14 wrong participant group, four ongoing trials and 18 secondary citations of excluded studies). Seven trials that were excluded for being in the wrong participant group ([Archimbaud 1999](#); [Geissler 2003](#); [Han 2015](#); [Higby 1974](#); [Miao 2012](#); [Moskowitz 2007](#); [Schiffer 2000](#)) were included in a separate review assessing alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ([Desborough 2016b](#)). In total, seven studies in 25 references were deemed eligible for inclusion ([Fricke 1991](#); [Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Mannucci 1986](#); [Platzbecker 2015](#); [Wang 2012](#)). The four ongoing trials are expected to be reported ([EudraCT 2010-022890-33](#); [EudraCT 2014-000174-19](#); [NCT02099747](#); [NCT02158936](#)).

## Included studies

Seven completed trials reported in 25 papers were included in the analysis (see [Characteristics of included studies](#) for full details of each study).

## Design

Seven trials were published as full-text articles (published in 25 papers) between 1986 and 2015 ([Fricke 1991](#); [Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Mannucci 1986](#); [Platzbecker 2015](#); [Wang 2012](#)). All seven were published in English. Three trials were parallel group two-arm trials ([Giagounidis 2014](#); [Greenberg 2013](#); [Platzbecker 2015](#)), two were parallel group three-arm trials ([Kantarjian 2010](#); [Wang 2012](#)) and two were cross-over trials ([Fricke 1991](#); [Mannucci 1986](#)).

## Sample sizes

The trials included 472 participants with numbers ranging from eight ([Fricke 1991](#); [Mannucci 1986](#)) to 250 ([Giagounidis 2014](#)).

## Setting

Four trials were conducted in the USA ([Fricke 1991](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)), one was conducted in Italy and Spain ([Mannucci 1986](#)), one was conducted in Australia, Canada, France, Germany, Italy, Poland, UK and the USA ([Giagounidis 2014](#)), and one was conducted in Brazil, Denmark, France, Germany, Hong Kong, Italy, South Korea, Taiwan, UK and the USA ([Platzbecker 2015](#)).

## Participants

Four trials included only participants with MDS ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)), one included participants with MDS and AML if no intensive treatment was planned ([Platzbecker 2015](#)), one included aplastic anaemia and MDS ([Fricke 1991](#)) and one included aplastic anaemia and familial thrombocytopenia ([Mannucci 1986](#)). In two trials, participants were not receiving chemotherapy ([Giagounidis 2014](#); [Platzbecker 2015](#)), in three trials participants were treated with low-dose chemotherapy: azacitidine ([Kantarjian 2010](#)), decitabine ([Greenberg 2013](#)) and lenalidomide ([Wang 2012](#)). In two trials, it was unclear if participants were receiving any other treatment ([Fricke 1991](#); [Mannucci 1986](#)).

## Interventions

All the interventions included in the review reduce platelet transfusion rather than replace it directly. Four trials compared romiplostim with placebo ([Giagounidis 2014](#); [Greenberg 2013](#); [Kantarjian 2010](#); [Wang 2012](#)), and one trial compared eltrombopag with placebo ([Platzbecker 2015](#)). Two trials used weekly subcutaneous romiplostim 750 µg ([Giagounidis 2014](#); [Greenberg 2013](#)), two trials used weekly subcutaneous romiplostim 500 µg and romiplostim 750 µg ([Kantarjian 2010](#); [Wang 2012](#)), and one trial used daily oral eltrombopag 50 mg once daily, which was increased every two weeks based on the patients' platelet and peripheral bone marrow blast counts (doses of 100 mg, 200 mg and 300 mg, or 100 mg and 150 mg for patients of East Asian heritage) ([Platzbecker 2015](#)). In one trial, treatment continued for 26 weeks, followed by a four-week washout, then an optional continuation of 24 weeks (using the same treatment as at the initial randomisation) followed by another four-week washout ([Giagounidis 2014](#)). One trial continued treatment for 26 weeks followed by an optional additional 26 weeks ([Platzbecker 2015](#)). One trial continued treatment for the duration of four cycles of decitabine: approximately 16 to 24 weeks ([Greenberg 2013](#)), one trial continued treatment for the duration of four cycles of azacitidine: approximately 16 weeks, and one trial continued treatment for the duration of four cycles of lenalidomide: approximately 16 weeks ([Wang 2012](#)).

One trial compared tranexamic acid versus placebo ([Fricke 1991](#)), and one compared desmopressin (DDAVP) with placebo ([Mannucci 1986](#)).

No trials assessed artificial platelet substitutes, platelet-poor plasma, rFVIIa, rFXIII, interleukin 6, interleukin 11, fibrinogen concentrate.

## Outcomes

No trial reported all the outcomes of interest. Four trials reported data for our primary outcome of number and severity of bleeding episodes (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). Five trials also reported overall mortality, death from bleeding, platelet transfusions and adverse events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). Four trials reported risk of death from infection (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) and one reported red cell transfusion requirements (Platzbecker 2015). One trial did not report any outcomes of interest (Mannucci 1986), and one trial did not report any outcomes in a way that could be interpreted due to methodological flaws in the trial design (Fricke 1991).

## Incidence of bleeding and platelet transfusion

The incidence of bleeding in the control arms of the five trials of thrombopoietin (TPO) mimetics ranged from 8% (Wang 2012) to 54% (Kantarjian 2010). The proportion of participants receiving a platelet transfusion in the control arms of the five trials of TPO mimetics ranged from 33% (Wang 2012) to 79% (Platzbecker 2015). The trials of DDAVP versus placebo (Mannucci 1986) and tranexamic acid versus placebo (Fricke 1991) did not report sufficient detail of the burden of bleeding or platelet transfusion in these groups.

## Excluded studies

We excluded 67 studies from the review (See [Characteristics of excluded studies](#) for further details).

- Two studies were review articles (NIHR 2014; Reynolds 2000).
- Twenty-six studies were not randomised controlled trials (ACTRN12610000641099; Antun 2013; Castamann 1997; Cattani 1963; Desmond 2014; Dickinson 2014; EudraCT

2012-004886-42; Fenaux 2013; Gerrits 2015; Gordon 1995; Kantarjian 2007; Kantarjian 2012; Kurzrock 2001; Mittelman 2012; Montero 2006; NCT01286038; NCT01481220; Olnes 2012; Pecci 2010; Perez Ruixo 2012; Ramadan 2015; Schrezenmeier 1995; Sekeres 2009; Svensson 2014; Will 2009; Young 1997).

- Three studies were incorrect interventions (Khan 2015; NCT01893372; NCT02094417).
- Fourteen were trials on the wrong participant group (Archimbaud 1999; Bussel 2007; Chen 2010; Geissler 2003; Giles 2005; Han 2015; Higby 1974; ISRCTN73545489; Miao 2012; Moskowitz 2007; NCT02094248; NCT02578901; Schiffer 2000; Usuki 2007).
- Four ongoing studies (EudraCT 2010-022890-33; EudraCT 2014-000174-19; NCT02099747; NCT02158936).
- Eighteen studies were secondary citations for excluded studies.

## Ongoing studies

We identified four ongoing studies (see [Characteristics of ongoing studies](#)) (EudraCT 2010-022890-33; EudraCT 2014-000174-19; NCT02099747; NCT02158936). We will monitor the progress of these trials and on publication (assuming eligibility), we will include them in future updates of this review. Two trials are due to be completed by December 2020 (NCT02099747; NCT02158936). Two trials have not reported an expected completion date (EudraCT 2010-022890-33; EudraCT 2014-000174-19). All four of the ongoing studies are comparing eltrombopag versus placebo in the following settings: low/intermediate risk MDS (EudraCT 2010-022890-33), intermediate/high-risk MDS in combination with azacitidine (NCT02158936), moderate aplastic anaemia (EudraCT 2014-000174-19) and severe/very severe aplastic anaemia (NCT02099747). These trials are planning to include 837 participants in total.

## Risk of bias in included studies

See the 'Risk of bias' tables within [Characteristics of included studies](#) for details of our assessment for each study and [Figure 2](#) for a tabular summary.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fricke 1991	?	?	?	?	-	-	-
Giagounidis 2014	?	+	?	?	?	+	-
Greenberg 2013	?	?	+	+	+	+	-
Kantarjian 2010	?	?	?	?	+	+	-
Mannucci 1986	+	+	+	+	+	?	?
Platzbecker 2015	+	+	+	+	+	-	-
Wang 2012	?	+	+	+	+	+	-

## Allocation

## Sequence generation

## Thrombopoietin mimetics

### *Romiplostim*

Four trials were assessed at unclear risk of bias because they did not report details of the randomisation sequence (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012).

### *Eltrombopag*

The trial of eltrombopag was at low risk of bias because it used a permuted block randomisation schedule (Platzbecker 2015).

## Tranexamic acid

The trial of tranexamic acid versus placebo was at unclear risk of bias as it did not report sufficient information on sequence generation for a judgement to be made (Fricke 1991).

## DDAVP

The trial of DDAVP versus placebo was considered to be at low risk of bias as it used a computer-generated randomisation sequence (Mannucci 1986).

## Concealment of treatment allocation

## Thrombopoietin mimetics

### *Romiplostim*

Two trials were at low risk of bias because they used an interactive voice response system (Giagounidis 2014; Wang 2012). Two trials were considered at unclear risk of bias because they did not report sufficient details about concealment of treatment allocation (Greenberg 2013; Kantarjian 2010).

### *Eltrombopag*

The trial of eltrombopag versus placebo was considered to be at low risk of bias as it used an interactive voice response system (Platzbecker 2015).

## Tranexamic acid

The trial of tranexamic acid versus placebo was considered to be at unclear risk of bias as insufficient information was reported for concealment of treatment allocation to be assessed (Fricke 1991).

## DDAVP

The trial of DDAVP versus placebo was considered at low risk of bias, as it used sealed envelopes for concealment of treatment allocation (Mannucci 1986)

## Blinding

## Performance Bias

## Participants

## Thrombopoietin mimetics

### *Romiplostim*

Two trials were at low risk of bias as the methodology for blinding of participant was adequate (Greenberg 2013; Wang 2012). Two trials were at unclear risk of bias as they stated they were double-blind, placebo-controlled trials but did not provide details of the methodology (Giagounidis 2014; Kantarjian 2010).

### *Eltrombopag*

The trial of eltrombopag versus placebo was considered to be at low risk of bias as the methodology for blinding of participants was adequate (Platzbecker 2015).

### **Tranexamic acid**

The trial of tranexamic acid versus placebo was considered at unclear risk of bias. It was double-blinded and tranexamic acid and placebo were identical in appearance. However, tranexamic acid levels were taken weekly and before transfusion. Overall success of tranexamic acid was defined as either five failures of placebo and none of tranexamic acid or seven failures of placebo and one of tranexamic acid. Overall failure of tranexamic acid was defined as two failed courses of tranexamic acid. Sequential courses continued until overall success or failure of tranexamic acid could be determined. It is unclear how this assessment was performed without unblinding the analysis (Fricke 1991).

### **DDAVP**

The trial of DDAVP versus placebo was considered to be at low risk of bias as it was a double-blind, placebo-controlled trial with matching intervention and placebo (Mannucci 1986).

### **Study Personnel**

### **Thrombopoietin mimetics**

#### ***Romiplostim***

Two trials were at low risk of bias as methodology for blinding of participant was adequate (Greenberg 2013; Wang 2012). Two trials were at unclear risk of bias as they stated they were double-blind, placebo-controlled trials but did not provide details of the methodology (Giagounidis 2014; Kantarjian 2010).

#### ***Eltrombopag***

The trial of eltrombopag versus placebo was considered at low risk of bias as the methodology for blinding of study personnel was adequate (Platzbecker 2015).

### **Tranexamic acid**

The trial of tranexamic acid versus placebo was considered to be at unclear risk of bias. It was double-blinded and tranexamic acid and placebo were identical in appearance. However, tranexamic acid levels were taken weekly and before transfusion. Overall success of tranexamic acid was defined as either five failures of placebo and none of tranexamic acid or seven failures of placebo and one of tranexamic acid. Overall failure of tranexamic acid was defined as two failed courses of tranexamic acid. Sequential courses continued until overall success or failure of tranexamic acid could be

determined. It is unclear how this assessment was performed without unblinding the analysis (Fricke 1991).

### **DDAVP**

The trial of DDAVP versus placebo was considered at low risk of bias as it was a double-blind, placebo-controlled trial with matching intervention and placebo (Mannucci 1986).

### **Blinding of study analysts**

### **Thrombopoietin mimetics**

#### ***Romiplostim***

Two trials were at low risk of bias as methodology for blinding of study analysts was adequate (Greenberg 2013; Wang 2012). Two trials were at unclear risk of bias as they stated they were double-blind placebo-controlled trials but did not provide details of the methodology (Giagounidis 2014; Kantarjian 2010).

#### ***Eltrombopag***

The trial of eltrombopag versus placebo was considered to be at low risk of bias as methodology for blinding of study analysts was adequate (Platzbecker 2015).

### **Tranexamic acid**

The trial of tranexamic acid versus placebo was considered to be at unclear risk of bias. It was double-blinded and tranexamic acid and placebo were identical in appearance. However, tranexamic acid levels were taken weekly and before transfusion. Overall success of tranexamic acid was defined as either five failures of placebo and none of tranexamic acid or seven failures of placebo and one of tranexamic acid. Overall failure of tranexamic acid was defined as two failed courses of tranexamic acid. Sequential courses continued until overall success or failure of tranexamic acid could be determined. It is unclear how this assessment was performed without unblinding the analysis (Fricke 1991).

### **DDAVP**

The trial of DDAVP versus placebo was considered to be at low risk of bias as it was a double-blind placebo-controlled trial with matching intervention and placebo (Mannucci 1986).

## Incomplete outcome data

### Thrombopoietin mimetics

#### *Romiplostim*

Three trials were considered to be at low risk of bias as they analysed data on an intention-to-treat basis and all participants were accounted for in the final analysis (Greenberg 2013; Kantarjian 2010; Wang 2012). One trial was considered at unclear risk of bias because it was stopped early (Giagounidis 2014).

#### *Eltrombopag*

The trial of eltrombopag versus placebo was considered at low risk of bias as it analysed data on an intention-to-treat basis and all participants were accounted for in the final analysis (Platzbecker 2015).

#### Tranexamic acid

In the trial of tranexamic acid versus placebo was considered at high risk of bias, as only three out of eight participants completed the study (Fricke 1991).

#### DDAVP

The trial of DDAVP versus placebo was considered to be at low risk of bias, as all participants were accounted for in the final analysis (Mannucci 1986).

## Selective reporting

### Thrombopoietin mimetics

#### *Romiplostim*

Four trials were considered to be at low risk of bias, as all pre-specified outcomes from their protocols were included in the final manuscript (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012).

#### *Eltrombopag*

The trial of eltrombopag versus placebo was considered to be at high risk of bias from selective outcome reporting, as it stated that quality of life would be assessed but this was not included in the final paper (Platzbecker 2015).

#### Tranexamic acid

The trial of tranexamic acid versus placebo was at high risk of bias as it stated that severity of bleeding would be assessed but this was not included in the final paper (Fricke 1991).

#### DDAVP

The trial of DDAVP versus placebo was considered to be at unclear risk of bias as the protocol was not available (Mannucci 1986).

## Other potential sources of bias

### Thrombopoietin mimetics

#### *Romiplostim*

Four trials were considered to be at high risk of bias because: in two trials at least one author had served on an advisory board and received honoraria from the drug company sponsor (Giagounidis 2014; Wang 2012); in one trial, one of the authors received payment from the sponsor for writing the manuscript (Greenberg 2013); and in four trials, each of the following was applicable to at least one author: received research funding, worked as a consultant, was an employee, or stockholder in the sponsoring company (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012). Systematic review evidence demonstrates that when clinical trials are sponsored by the manufacturing company, the results are favourable more commonly than when trials have other sources of funding. This potential bias can not be explained by standard 'Risk of bias' assessments (Lundh 2012).

#### *Eltrombopag*

The trial of eltrombopag versus placebo was considered to be at high risk of bias because each of the following was applicable to at least one author: served on an advisory board, received honoraria, received research funding, worked as a consultant, was an employee or stockholder in the sponsoring company (Platzbecker 2015).

## Tranexamic acid

The trial of tranexamic acid versus placebo was considered to be at high risk of bias as one patient was kept in the study even though they received HLA-matched platelets (this was pre-defined as a reason for treatment failure), whereas two other patients were withdrawn after commencing HLA-matched platelet transfusions. There was significant heterogeneity in the number of courses of treatment each patient received (zero to more than 20) (Fricke 1991).

## DDAVP

The trial assessing DDAVP versus placebo was considered to be at unclear risk of other sources of bias. Von Willebrand factor (vWF) levels were two to three times the expected level at baseline which may have reduced the effect of DDAVP, as DDAVP acts by increasing plasma vWF levels (Mannucci 1986).

## Effects of interventions

See: [Summary of findings for the main comparison Thrombopoietin mimetic versus placebo](#)

No trials assessed artificial platelet substitutes, platelet-poor plasma, rFVIIa, rFXIII, interleukin 6, interleukin 11 or fibrinogen concentrate.

There were five trials with 456 participants comparing TPO mimetics versus placebo (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). The type of TPO mimetic, dose and duration of administration varied between trials. One trial with eight participants assessed tranexamic acid compared with placebo (Fricke 1991) and one trial with eight participants compared DDAVP with placebo (Mannucci 1986). In the DDAVP trial, the only outcome reported was the bleeding time (Mannucci 1986). This is a test used to estimate bleeding tendency and is performed by making a small cut in a participant's forearm and timing how long it takes for the bleeding to stop. The bleeding time is no longer used as a clinical test, as it is not considered to be a reliable measure of bleeding risk (Lehman 2001). No clinical outcomes were reported in this trial, so it could not be included in the quantitative synthesis. We did not include the tranexamic acid trial in the quantitative synthesis due to significant methodological flaws: bleeding was not defined equally between the tranexamic acid and control group; only three out of eight

participants completed the trial; there was high risk of reporting bias; and 1/8 participants completed the trial despite meeting a pre-specified reason for exclusion (Fricke 1991).

## Network meta-analysis

We could not perform a network meta-analysis because the included studies had important differences in the baseline severity of disease for the participants and in the number of participants undergoing chemotherapy. Three trials only included participants undergoing low-dose chemotherapy (Greenberg 2013; Kantarjian 2010; Wang 2012) and two trials did not include participants undergoing chemotherapy (Giagounidis 2014; Platzbecker 2015). One trial included participants with AML in addition to MDS (Platzbecker 2015), whereas the other trials only included participants with MDS (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012). There was variation through all trials in the international prognostic scoring system (IPSS) of the participants included in the trials. This raised important concerns about the plausibility of the transitivity assumption in the final dataset and we could not evaluate transitivity statistically because of the small number of trials per comparison. Therefore, we could only perform direct pairwise meta-analyses of included interventions. Full details of the proposed methodology are included in [Differences between protocol and review](#). Consequently, only direct pairwise meta-analyses were performed and the results of these are described below.

## Thrombopoietin (TPO) mimetics

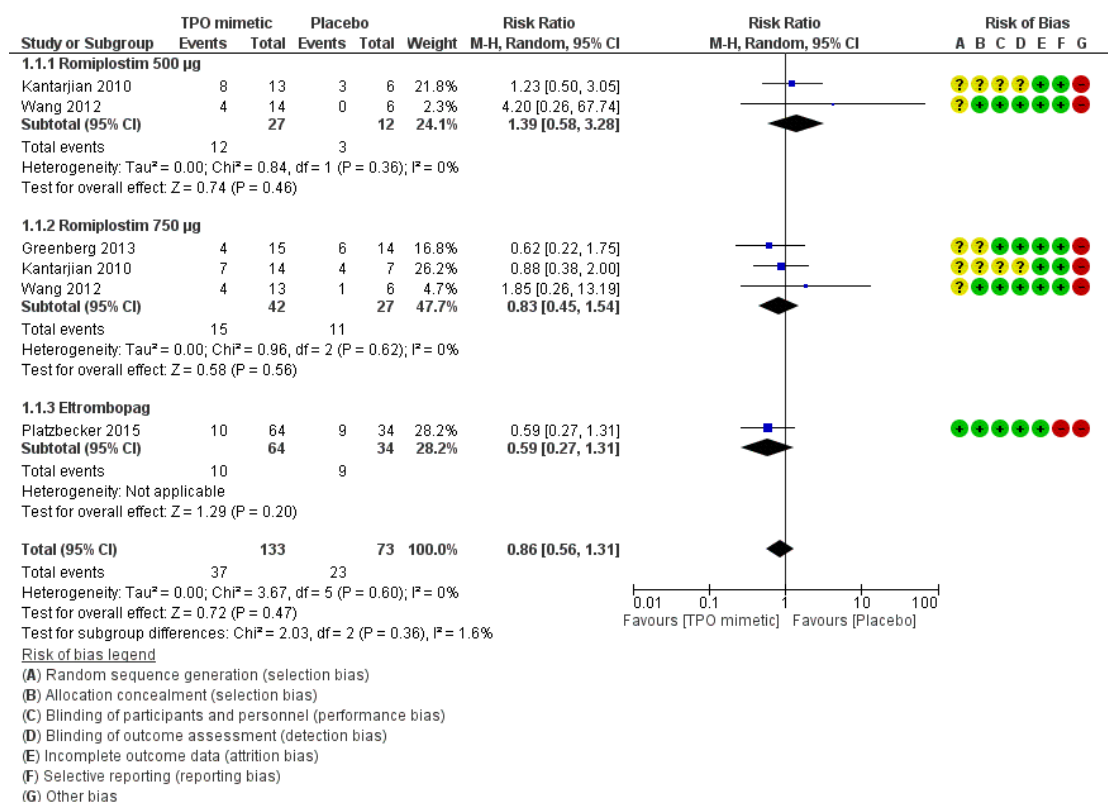
### Primary outcomes

#### The number of participants with at least one bleeding episode

Four trials (206 participants) reported the number of participants with at least one bleeding episode (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was insufficient evidence to detect a difference in the risk of a bleeding episode between those treated with a TPO mimetic and placebo (RR 0.86, 95% CI 0.56 to 1.31,  $I^2 = 0\%$ , four trials, 206 participants, *low-quality evidence*) (Analysis 1.1; Figure 3).



**Figure 3. Thrombopoietin mimetic versus placebo. Number of participants with at least one bleeding episode**



### Romiplostim

There was insufficient evidence to detect a difference in the number of participants with at least one bleeding episode between romiplostim 500 µg and placebo (RR 1.39, 95% CI 0.58 to 3.28,  $I^2 = 0\%$ , two trials, 39 participants) (Kantarjian 2010; Wang 2012), or romiplostim 750 µg and placebo (RR 0.83, 95% CI 0.45 to 1.54,  $I^2 = 23\%$ , three trials, 69 participants) (Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.1; Figure 3).

### Eltrombopag

There was insufficient evidence to detect a difference in the number of participants with at least one bleeding episode between eltrombopag and placebo (RR 0.59, 95% CI 0.27 to 1.31, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.1; Figure 3).

### The number of participants with at least one episode of severe or life-threatening bleeding

One trial (40 participants) reported the number of participants with at least one episode of severe or life-threatening bleeding (Kantarjian 2010). There was insufficient evidence to detect a difference in the risk of a life-threatening bleed between those treated with a TPO mimetic and placebo (RR 0.31, 95% CI 0.04 to 2.26, one trial, 40 participants, *low-quality evidence*) (Kantarjian 2010) (Analysis 1.2).

### Romiplostim

There was insufficient evidence to detect a difference in the risk of a life-threatening bleed between those treated with romiplostim 500 µg and placebo (RR 0.46, 95% CI 0.03 to 6.20, one trial, 19 participants) (Kantarjian 2010) or romiplostim 750 µg and placebo (RR 0.18, 95% CI 0.01 to 3.88, one trial, 21 participants) (Analysis 1.2).



## Eltrombopag

Outcome not reported.

## Number of days of bleeding per participant

Outcome not reported in any trial.

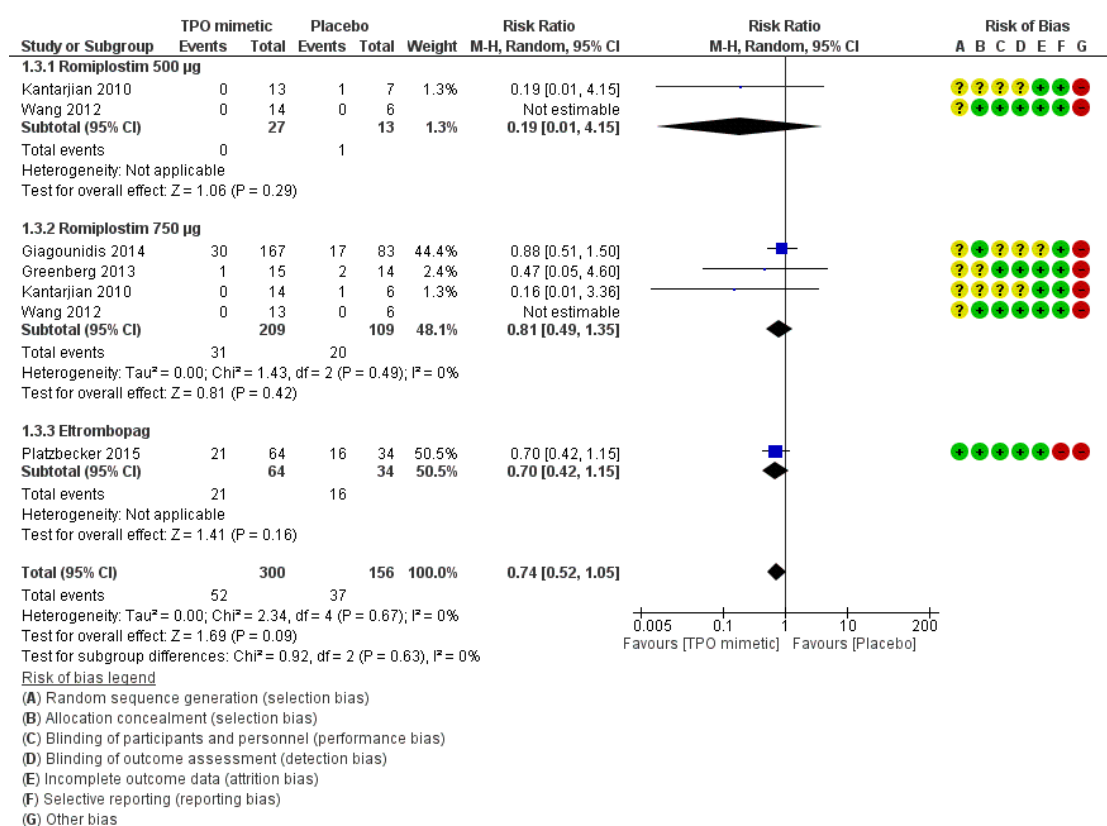
## Secondary outcomes

## Mortality

## All-cause mortality

Five trials (456 participants) reported all-cause mortality (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was insufficient evidence to detect a difference in the risk of all-cause mortality between those treated with a TPO mimetic and placebo (RR 0.74, 95% CI 0.52 to 1.05,  $I^2 = 0\%$ , five trials, 456 participants, *very low-quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) (Analysis 1.3; Figure 4).

**Figure 4. Thrombopoietin mimetic versus placebo. All-cause mortality.**



## Romiplostim

There was no evidence for a difference in all-cause mortality between romiplostim 500 µg and placebo (RR 0.19, 95%CI

0.19, 95% CI 0.01 to 4.15,  $I^2 = 0\%$ , two trials, 40 participants) (Kantarjian 2010; Wang 2012). There was no evidence for a difference in overall mortality between romiplostim 750 µg and placebo (RR 0.81, 95% CI 0.49 to 1.35,  $I^2 = 0\%$ , four trials, 318 par-

ticipants) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.3; Figure 4).

### *Eltrombopag*

There was no evidence for a difference in overall mortality between eltrombopag and placebo (RR 0.70, 95%CI 0.42 to 1.15, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.3; Figure 4).

### **Mortality due to bleeding**

Five trials (457 participants) reported mortality due to bleeding (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was no evidence for a difference in mortality due to bleeding between TPO mimetics and placebo (RR 0.44, 95% CI 0.07 to 2.69,  $I^2 = 38\%$ , five trials, 457 participants) (Analysis 1.4).

### *Romiplostim*

There were no deaths from bleeding in the intervention arms of either study assessing romiplostim 500  $\mu\text{g}$  (Kantarjian 2010; Wang 2012). There was no evidence for a difference in mortality from bleeding between romiplostim 750  $\mu\text{g}$  and placebo (RR 0.14, 95% CI 0.02 to 1.22  $I^2 = 0\%$ , four trials, 319 participants) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.4).

### *Eltrombopag*

There was no evidence for a difference in mortality due to bleeding between eltrombopag and placebo (RR 1.33, 95% CI 0.27 to 6.49, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.4).

### **Mortality due to infection**

Four trials (206 participants) reported mortality due to infection (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was no evidence for a difference in mortality due to infection between TPO mimetics and placebo (RR 0.62, 95% CI 0.32 to 1.19,  $I^2 = 0\%$ , four trials, 206 participants) (Analysis 1.5).

### *Romiplostim*

There was no evidence for a difference in mortality from infection between romiplostim 500  $\mu\text{g}$  and placebo (RR 0.19, 95% CI 0.01 to 4.15,  $I^2 = 0\%$ , two trials, 40 participants) (Kantarjian 2010; Wang 2012). There was no evidence for a difference in mortality from infection between romiplostim 750  $\mu\text{g}$  and placebo (RR 0.43, 95% CI 0.06 to 3.24,  $I^2 = 0\%$ , three trials, 68 participants) (Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.5).

### *Eltrombopag*

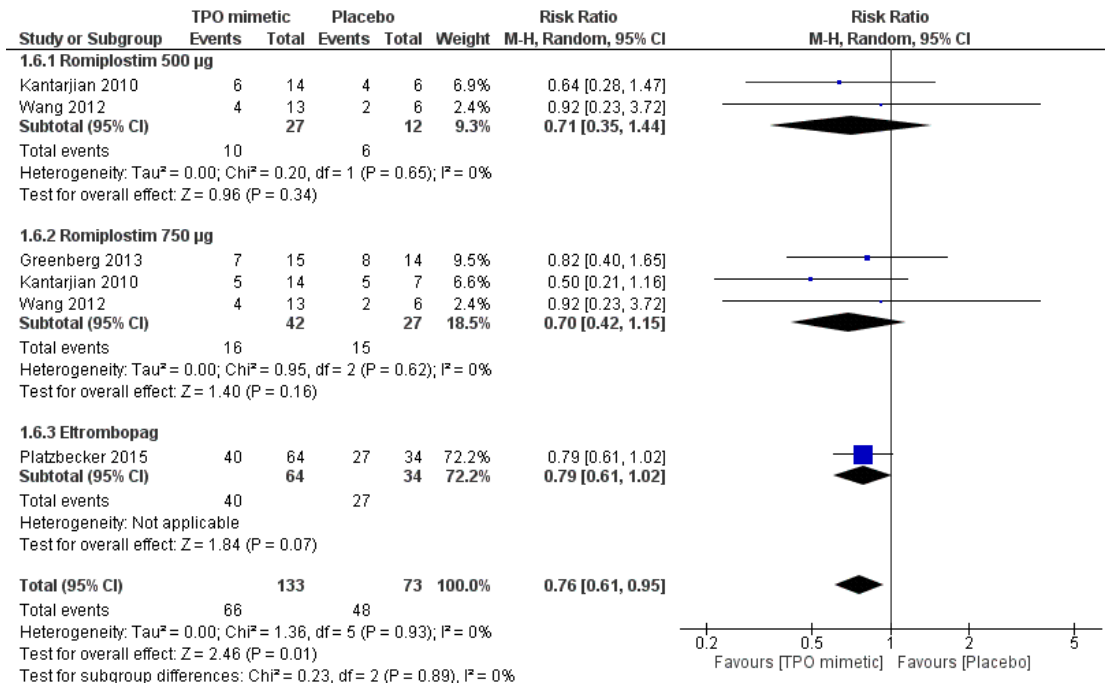
There was no evidence for a difference in mortality from infection between eltrombopag and placebo (RR 0.69, 95% CI 0.34 to 1.41, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.5).

### **Platelet transfusions**

#### **Proportion of participants requiring a platelet transfusion**

Four trials (206 participants) reported the proportion of patients requiring a platelet transfusion (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was a significant reduction in the number of platelet transfusions for those treated with TPO mimetics compared to placebo (RR 0.76, 95% CI 0.61 to 0.95,  $I^2 = 0$ , four trials, 206 participants, *moderate-quality evidence*) (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) (Analysis 1.6; Figure 5).

**Figure 5. Proportion of participants receiving a platelet transfusion.**



### *Romiplostim*

There was no evidence for a difference in the proportion of participants requiring a platelet transfusion between romiplostim 500 µg and placebo (RR 0.71, 95%CI 0.35 to 1.44, two trials, 39 participants) (Kantarjian 2010; Wang 2012) or romiplostim 750 µg and placebo (RR 0.70, 95% CI 0.42 to 1.15,  $I^2 = 0$ , three trials, 69 participants) (Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.6; Figure 5).

### *Eltrombopag*

There was no evidence for a difference in the proportion of participants requiring a platelet transfusion between eltrombopag and placebo (RR 0.79, 95% CI 0.61 to 1.02, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.6; Figure 5).

### Number of platelet units transfused per participant

Five trials (456 participants) reported platelet units transfused per participant but with insufficient information for combination into meta-analysis (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). Results are summarised in Table 1.

### Mean number of platelet transfusion episodes per participant

No trial reported mean number of platelet transfusion episodes as an outcome.

### Red cell transfusions

#### Proportion of participants requiring a red cell transfusion

No trial reported proportion of participants requiring a red cell transfusion.

#### Number of red cell units transfused per participant

One trial (98 participants) reported proportion of patients requiring a red cell transfusion but with insufficient information for combination into meta-analysis (Platzbecker 2015). Participants treated with eltrombopag received mean 4.8 units red blood cells whereas those treated with placebo received mean 6.3 units.

#### Mean number of red cell transfusion episodes per participant

No trial reported mean number of red cell transfusion episodes per participant.

## Adverse events

### Transfusion reactions

One trial reported transfusion reactions (Platzbecker 2015). There was no evidence for a difference in the incidence of transfusion reactions between those treated with eltrombopag and placebo (Peto odds ratio (pOR) 0.06, 95% CI 0.00 to 3.44, one trial, 98 participants, *very low-quality evidence*). The event rate was low with one transfusion reaction reported in total (Analysis 1.7).

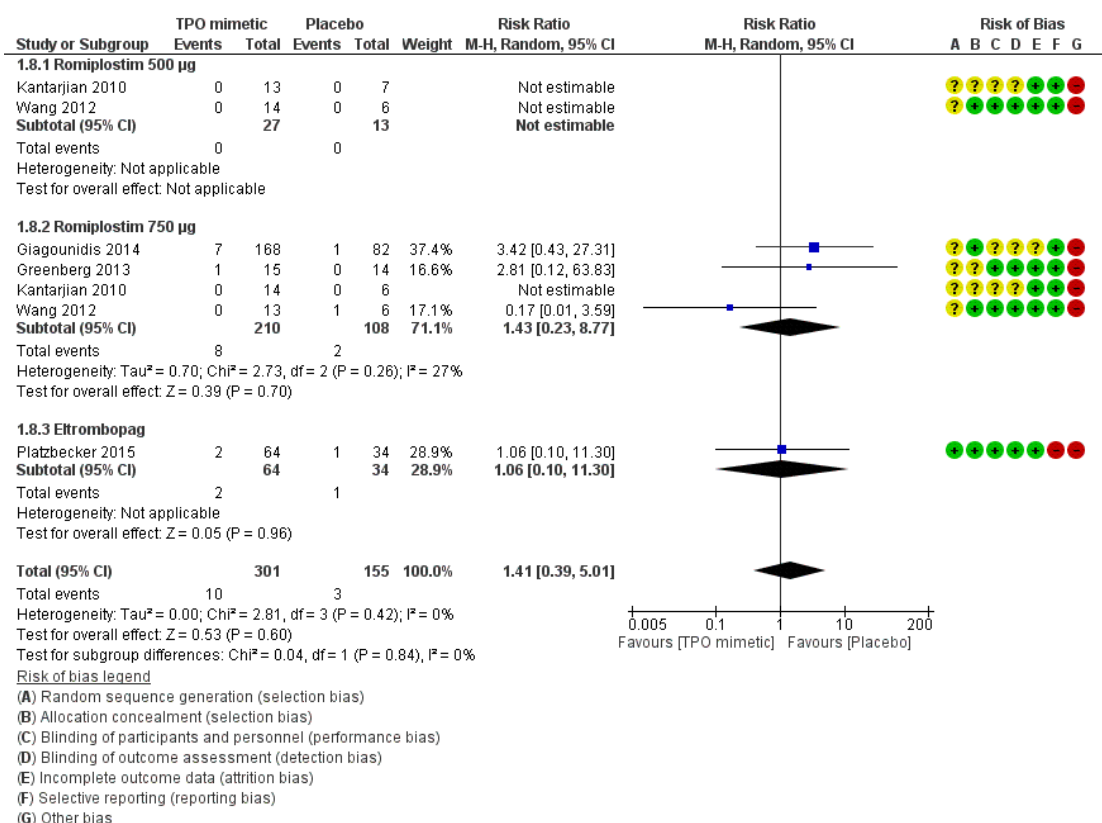
### Transfusion-transmitted infection

No trial reported transfusion-transmitted infection as an outcome.

### Thromboembolic events

Five trials (456 participants) reported thromboembolic events (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was no evidence for a difference in thromboembolic events between TPO mimetics and placebo (RR 1.41, 95% CI 0.39 to 5.01,  $I^2 = 0\%$ , five trials, 456 participants, *very low-quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) (Analysis 1.8; Figure 6).

**Figure 6. Thrombopoietin mimetic versus placebo. Thromboembolism.**



### Romiplostim

There were no thromboembolic events in either study assessing romiplostim 500 µg (Kantarjian 2010; Wang 2012). There was no

evidence for a difference in thromboembolic events between romiplostim 750 µg and placebo (RR 1.43, 95% CI 0.23 to 8.77,  $I^2 = 0\%$ , four trials, 318 participants) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.8; Figure 6)

### ***Eltrombopag***

There was no evidence for a difference in thromboembolic events between eltrombopag and placebo (RR 1.06, 95% CI 0.10 to 11.30, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.8; Figure 6).

### **Formation of anti-HLA antibodies**

No trial reported formation of anti-HLA antibodies as an outcome.

### **Platelet refractoriness**

No trial reported platelet refractoriness as an outcome.

### **Drug reactions**

Five trials (455 participants) reported drug reactions (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). There was no evidence for a difference in drug reactions between TPO mimetics and placebo (RR 1.12, 95% CI 0.83 to 1.51, five trials, 455 participants, *low-quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) (Analysis 1.9).

### ***Romiplostim***

There was no evidence for a difference in drug reactions between romiplostim 500 µg and placebo (RR 0.62, 95% CI 0.23 to 1.70,  $I^2 = 0\%$ , two trials, 40 participants) (Kantarjian 2010; Wang 2012) or romiplostim 750 µg and placebo (RR 1.17, 95% CI 0.80 to 1.70,  $I^2 = 0\%$ , four trials, 317 participants) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012) (Analysis 1.9).

### ***Eltrombopag***

There was no evidence for a difference in drug reactions between eltrombopag and placebo (RR 0.80, 95% CI 0.24 to 2.63, one trial, 98 participants) (Platzbecker 2015) (Analysis 1.9).

### **Tranexamic acid**

There was one trial of tranexamic acid versus placebo (Fricke 1991). We extracted no data from this study due to major methodological problems in the study design. In addition to the high risk of bias in terms of attrition bias, reporting bias and other bias (see text section above, Figure 2 and the Risk of bias in included studies table), there was a variable number of study cycles depending on the results of previous cycles of treatment. All these factors meant that it was impossible to fully understand the data in this trial and

we took the decision not to include this trial in the assessment of 'effects of interventions'.

### **DDAVP**

There was one trial of DDAVP versus placebo (Mannucci 1986). This study had a single outcome: bleeding time. It did not assess any of the outcomes of interest in this review. Consequently, no data could be extracted from this trial.

## **DISCUSSION**

### **Summary of main results**

### **Network meta-analysis**

We could not perform a network meta-analysis because the included studies had important differences in the baseline severity of disease for the participants, and in the number of participants undergoing chemotherapy. This raised important concerns about the plausibility of the transitivity assumption in the final dataset and we could not evaluate transitivity statistically because of the small number of trials per comparison. Therefore, we could only perform direct pairwise meta-analyses of included interventions.

### **Pairwise meta-analysis**

Each of the interventions identified in this review have the potential to reduce platelet transfusion, but are not direct alternatives.

### **Thrombopoietin (TPO) mimetics**

Five trials reported in 23 papers reported the use of TPO mimetics (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

### **Efficacy**

There was insufficient evidence to detect a difference in the number of participants with at least one bleeding episode between TPO mimetics and placebo (RR 0.86, 95% CI 0.56 to 1.31, four trials, 206 participants, *low-quality evidence*) (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

There was insufficient evidence to detect a difference in the risk of a life-threatening bleed between those treated with a TPO mimetic and placebo (RR 0.31, 95% CI 0.04 to 2.26, one trial, 40 participants, *low-quality evidence*) (Kantarjian 2010). Severe or life-threatening bleeding events were rare and consequently, the quality of the evidence was reduced by imprecision. There was a small

improvement in the RR of severe or life-threatening bleeding as the romiplostim dose increased but the event numbers were too low to assess if this is a dose-related effect.

There was insufficient evidence to detect a difference in the risk of all-cause mortality between those treated with a TPO mimetic and placebo (RR 0.74, 95% CI 0.52 to 1.05, five trials, 456 participants, *very low-quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

There was insufficient evidence to detect a difference in mortality from bleeding (RR 0.44, 95% CI 0.07 to 2.69, five trials, 457 participants) or mortality from infection (RR 0.62, 95% CI 0.32 to 1.19, four trials, 206 participants) (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012) between those treated with TPO mimetics and placebo.

There was a significant reduction in the number of participants receiving any platelet transfusion between those treated with TPO mimetics and placebo (RR 0.76, 95% CI 0.61 to 0.95, four trials, 206 participants, *moderate-quality evidence*) (Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). Data for units of platelets and units of red blood cells per participant were not reported adequately for meta-analysis.

### Adverse events

There was no evidence for a difference in the incidence of transfusion reactions between those treated with TPO mimetics and placebo (Peto odds ratio (pOR) 0.06, 95% CI 0.00 to 3.44, one trial, 98 participants, *very low-quality evidence*) (Platzbecker 2015), but with only a single reported transfusion reaction, interpretation of this finding is limited by imprecision.

There was no evidence for a difference in thromboembolic events between TPO mimetics and placebo (RR 1.41, 95% CI 0.39 to 5.01, five trials, 456 participants, *very low-quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

There was no evidence for a difference in drug reactions between TPO mimetics and placebo (RR 1.12, 95% CI 0.83 to 1.51, five trials, 455 participants, *low quality evidence*) (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012).

No trial reported number of days bleeding per participant, platelet transfusion episodes, mean red cell transfusions per participant, red cell transfusion episodes, transfusion-transmitted infections, formation of antiplatelet antibodies or platelet refractoriness.

### Tranexamic acid

One trial reported tranexamic acid (Fricke 1991). We did not include this trial in the quantitative synthesis due to significant methodological flaws: bleeding was not defined equally between the tranexamic acid and control group; only three out of eight participants completed the trial; there was high risk of reporting

bias; and 1/8 participants completed the trial despite meeting a pre-specified reason for exclusion.

### DDAVP

One trial reported DDAVP (Mannucci 1986). The only outcome reported in this trial was the bleeding time. This is a test used to estimate bleeding tendency and is performed by making a small cut in a participant's forearm and timing how long it takes for the bleeding to stop. The bleeding time is no longer used as a clinical test, as it is not considered to be a reliable measure of bleeding risk (Lehman 2001). No clinical outcomes were reported in this trial, so it was not included in the quantitative synthesis.

### Other agents

No trial assessed artificial platelets, platelet-poor plasma, activated factor VII, fibrinogen concentrate or recombinant interleukin 6 or 11. The remainder of this discussion will focus only on TPO mimetic as there is inadequate trial data for assessing the other interventions.

### Overall completeness and applicability of evidence

Four trials only included participants with MDS and one included participants with MDS and AML. The severity of MDS varied between trials. One trial planned to only include IPSS low and intermediate-1 MDS, but recruited one participant with IPSS intermediate-2 disease (Giagounidis 2014). Three trials aimed to recruit participants with IPSS low, intermediate-1 and intermediate-2 risk disease (Greenberg 2013; Kantarjian 2010; Wang 2012), although one of these trials recruited a single participant with IPSS high-risk disease (Greenberg 2013). One trial did not use the IPSS classification but included relatively high-risk MDS (refractory anaemia with an excess of blasts) and AML (Platzbecker 2015). No participants with aplastic anaemia or congenital bone marrow failure conditions were included. Two trials excluded participants receiving chemotherapy (Giagounidis 2014; Platzbecker 2015). The remaining three trials included participants who were receiving low-dose chemotherapy: azacitidine (Kantarjian 2010), decitabine (Greenberg 2013) and lenalidomide (Wang 2012). All of the trials only included adults. No trials assessed artificial platelets, platelet-poor plasma, activated factor VII, fibrinogen concentrate or recombinant interleukin 6 or 11. Trials were identified of tranexamic acid (data not extracted because of methodological flaws) (Fricke 1991) and DDAVP (data not extracted as none of the outcomes of interest in this review were reported) (Mannucci 1986).

Four trials (206 participants) reported the number of participants with any bleeding episode. There was no evidence for a difference in this outcome and in order to demonstrate a reduction in number of participants with any bleeding episode from 26 in 100 to 16 in



100 participants (as seen in the eltrombopag data), a study would need to recruit 514 participants (80% power, 5% significance). Eight hundred and thirty-seven further participants are due to be recruited into future trials by December 2020, 451 of which are of eltrombopag in MDS, so this question may be answered when these data are available.

One trial (40 participants) reported the number of participants with a severe/life-threatening bleeding episode. There was no evidence for a difference in the risk of severe/life-threatening bleeding between TPO mimetics and placebo. In order to demonstrate a reduction in severe or life-threatening bleeding events from 15 in 100 to 8 in 100 (as seen with romiplostim 500 µg), a study would need to recruit 646 participants (80% power, 5% significance). This question may be answered once the four ongoing trials are completed.

Five trials (456 participants) reported overall mortality. There was no evidence for a difference in the risk of overall mortality between those treated with TPO mimetics and placebo. In order to demonstrate a reduction in overall mortality from 24 in 100 to 19 in 100 (as seen with the pooled TPO mimetic data), a study would need to recruit 2114 participants (80% power, 5% significance) and consequently, even with the additional data provided by the four ongoing trials, this question is unlikely to be answered.

Four trials (206 participants) reported the number of participants who received a platelet transfusion. A reduction was noted in the number of participants who received a platelet transfusion between those treated with TPO mimetics and placebo. In order to demonstrate a reduction in number of participants who received a platelet transfusion from 66 in 100 to 50 in 100 (as seen with the pooled TPO mimetic data), a study would need to recruit 292 participants (80% power, 5% significance). Consequently, these studies are close to being adequately powered and it would be expected that this question will be answered when the ongoing trials have been reported. A reduction in the number of participants receiving platelet transfusion would be clinically significant.

Transfusion reactions were rare events with only a single reaction recorded in any trial. It is unlikely that a significant difference will be found in transfusion reactions, even once future trials are published. Five trials (456 participants) reported thromboembolism. We found no evidence for a difference in the risk of thromboembolism between participants treated with a TPO mimetics and control. In order to detect an increase in thrombosis incidence from 2 in 100 to 4 in 100 (as seen with the pooled TPO mimetic data), a study would need to recruit 2278 participants (80% power, 5% significance). Even with the addition of data from the ongoing trials, there will be insufficient data to determine if this increase in the risk of thromboembolism is present.

Five trials (455 participants) reported drug reactions. No significant difference was found between the groups. Five trials (455 participants) reported units of platelets per participant and one trial (98 participants) reported number of participants with at least one red cell transfusion, but not in a way that could be incorporated

into meta-analysis.

No trial reported days of bleeding per participant, platelet transfusion episodes, mean red cell transfusions per participant, red cell transfusion episodes, transfusion-transmitted infections, formation of antiplatelet antibodies or platelet refractoriness.

## Quality of the evidence

We considered all trials of TPO mimetics to be at high risk of bias because in three trials at least one author had served on an advisory board and received honoraria from the drug company sponsor (Giagounidis 2014; Platzbecker 2015; Wang 2012); in one trial, one of the authors received payment from the sponsor for writing the manuscript (Greenberg 2013) and in five trials, at least one author had received research funding, worked as a consultant, was an employee, and stockholder in the sponsoring company (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Platzbecker 2015; Wang 2012). Systematic review evidence demonstrates that when clinical trials are sponsored by the manufacturing company, the results are favourable more commonly than when trials have other sources of funding. This potential bias can not be explained by standard 'Risk of bias' assessments (Lundh 2012). One trial was also considered to be at risk of reporting bias, as it did not report all the outcomes prespecified in its protocol (Platzbecker 2015). Consequently, we downgraded all outcomes one point for risk of bias (Figure 2).

We did not downgrade the number of platelet transfusions per participant for imprecision, as it was close to being adequately powered. We downgraded all other outcomes one point for imprecision as they were underpowered. We downgraded overall mortality, transfusion reactions and thromboembolism two points due to imprecision.

We downgraded transfusion reactions one point due to indirectness, as this outcome was dependent on a significant difference in the number of blood component transfusions between those receiving TPO mimetics and placebo. A full summary of quality of the evidence is included in [Summary of findings for the main comparison](#).

## Potential biases in the review process

There were no obvious biases within the review process. We conducted a wide search and the relevance of each paper identified was carefully assessed, and no restrictions were made for the language in which the paper was originally published. Original authors and sponsors were given the opportunity to provide additional data to clarify the results of their trials but none put forward any new information. We could not formally assess publication bias, as our primary outcomes were reported in four papers, and only for trials assessing TPO mimetics. The interim results of one ongoing trial were published in 2012 but we do not believe this represents pub-

lication bias because we are not expecting the trial to be published until at least 2019 (the trial opened in France in June 2014 and follow-up for individual participants is for five years) (EudraCT 2010-022890-33).

## Agreements and disagreements with other studies or reviews

A systematic review and meta-analysis of TPO mimetics for MDS published in 2014 (Prisca 2014), assessed the same four trials of romiplostim that were included in this review (Giagounidis 2014; Greenberg 2013; Kantarjian 2010; Wang 2012). At the time of publication of that review no data had been published on eltrombopag. The authors noted no evidence for a difference in the risk of bleeding between those treated with romiplostim and placebo, although they did note a reduction in expose-adjusted bleeding rate. They also noted a reduction in exposure adjusted platelet transfusion rate. With the exception of number of participants receiving any platelet transfusion, these meta-analyses are underpowered and the results of ongoing studies are likely to lead to adequately powered meta-analysis for bleeding risk. A further detailed systematic review of TPO mimetics in MDS is presently underway (Dodillet 2012).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is inadequate evidence to recommend the use of thrombopoietin (TPO) mimetics for bone marrow failure, although the results of four ongoing trials may change this. There is moderate quality evidence that TPO mimetics reduce the number of partic-

ipants requiring a platelet transfusion compared to placebo. However further data will be necessary in order to assess other clinical outcomes. One randomised trial of tranexamic acid versus placebo, and one randomised controlled trial of desmopressin (DDAVP) versus placebo were identified but neither trial was reported in a way that allowed the extraction of any clinical data. There were no randomised controlled trials assessing artificial platelet substitutes, platelet-poor plasma, rFVIIa, rFXIII, interleukin 6, interleukin 11 or fibrinogen concentrate for people with bone marrow failure.

### Implications for research

Our search strategy has identified four further trials of TPO mimetics (eltrombopag) with 837 participants, which are presently underway for people with bone marrow failure. In order to demonstrate a fall in bleeding events from 26 in 100 to 16 in 100 participants (as seen in the eltrombopag data), a study would need to recruit 514 participants (80% power, 5% significance) and it is likely that the publication of additional data from ongoing trials will answer this question. There are no adequate randomised controlled trials assessing artificial platelet substitutes, platelet-poor plasma, rFVIIa, rFXIII, interleukin 6, interleukin 11, fibrinogen concentrate, DDAVP or antifibrinolytics for people with bone marrow failure and this remains a potential area for future research.

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**References to other published versions of this review****Desborough 2016c**

Desborough M, Estcourt LJ, Chaimani A, Doree C, Hopewell S, Trivella M, et al. Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with thrombocytopenia due to chronic bone marrow failure: a network meta-analysis and systematic review. *Cochrane Database of Systematic Reviews* 2016, Issue 1. [DOI: 10.1002/14651858.CD012055]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

Fricke 1991

Methods	<p><b>Type of study:</b> Single centre, two-arm, cross-over randomised controlled trial</p> <p><b>Countries where study was performed:</b> USA</p> <p><b>Dates of trial:</b> Not reported</p> <p><b>Follow-up until:</b> Up to 2 years</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• “Amegakaryocytic thrombocytopenia”</li> <li>• Platelet count <math>&lt; 20 \times 10^9/L</math> with no immediate prospect of recovery and absent/rare megakaryocytes in the bone marrow aspirate/biopsy</li> <li>• At least 1 bleeding episode per month (excluding skin bleeding)</li> <li>• A history of platelet transfusions for such bleeding episodes</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Active bleeding from an anatomical lesion (e.g. peptic ulcer)</li> <li>• Personal or family history of hypercoagulopathy</li> <li>• Pregnancy</li> <li>• Disseminated intravascular coagulation</li> <li>• Liver failure</li> <li>• Personal history of a congenital bleeding disorder</li> </ul> <p><b>Number of participants randomised:</b> 8</p> <p><b>Number of participants analysed:</b> 8</p> <p><b>Age:</b> Not reported</p> <p><b>Gender:</b> Not reported</p> <p><b>Types of malignancy:</b> Aplastic anaemia: 7, myelodysplastic syndrome: 1</p> <p><b>Chemotherapy regimens:</b> Not reported</p>
Interventions	<p><b>Intervention arm:</b> Tranexamic acid (20 mg/kg) 3 x daily for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. Placebo (equivalent number of identical placebo tablets) for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. The method of allocating the randomised patients to further courses of tranexamic acid or placebo was not stated</p> <p><b>Comparator arm:</b> Placebo (equivalent number of identical placebo tablets) for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. Tranexamic acid (20 mg/kg) 3 x daily for 4 weeks or until a platelet transfusion was required to control bleeding. Followed by a 1-week rest period. The method of allocating the randomised patients to further courses of tranexamic acid or placebo was not stated</p>

Outcomes	<b>Primary outcome:</b> <ul style="list-style-type: none"><li>Defined overall success of tranexamic acid in a participant as either 5 failures of placebo and none of drug or 7 failures of placebo and 1 of drug. Defined overall failure of tranexamic acid as 2 failed courses of drug. Sequential courses continued until overall success or failure of tranexamic acid could be determined.</li></ul> <b>Secondary outcomes:</b> <ul style="list-style-type: none"><li>Number of bleeding episodes</li><li>Severity of bleeding episodes</li><li>Site of bleeding episodes</li><li>Platelet transfusion requirement</li><li>Red cell transfusion requirement</li><li>Drug side effects</li></ul>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	No information on random sequence generation, although states that participants were randomised. Unclear if participants were re-randomised after initial two courses of treatment
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment, although states that participants were randomised
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was double-blinded and tranexamic acid and placebo were identical in appearance. However, tranexamic acid levels were taken weekly and before transfusion. Overall success of tranexamic acid was defined as either 5 failures of placebo and none of tranexamic acid or 7 failures of placebo and 1 of tranexamic acid. Overall failure of tranexamic acid was defined as 2 failed courses of tranexamic acid. Sequential courses continued until overall success or failure of tranexamic acid could be determined. It is unclear how this assessment was performed without unblinding the analysis.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was double-blinded and tranexamic acid and placebo were identical in appearance. However, tranexamic acid levels were taken weekly and before transfusion.

**Fricke 1991** (Continued)

		Overall success of tranexamic acid was defined as either 5 failures of placebo and none of tranexamic acid or 7 failures of placebo and 1 of tranexamic acid. Overall failure of tranexamic acid was defined as 2 failed courses of tranexamic acid. Sequential courses continued until overall success or failure of tranexamic acid could be determined. It is unclear how this assessment was performed without unblinding the analysis.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 3 out of 8 participants completed the randomised section of the study
Selective reporting (reporting bias)	High risk	Severity of bleeding was not reported, although it was listed as an outcome in the methods
Other bias	High risk	One patient was kept in the study even though they received HLA-matched platelets (this was pre-defined as a reason for treatment failure), whereas two other patients were withdrawn after commencing HLA-matched platelet transfusions. There was significant heterogeneity in the number of courses of treatment each patient received (0 to more than 20)

**Giagounidis 2014**

Methods	<p><b>Type of study:</b> Multi-national, multi-centre, parallel groups two-arm, randomised controlled trial</p> <p><b>Countries where study was performed:</b> Australia, Canada, France, Germany, Italy, Poland, UK, USA</p> <p><b>Dates of trial:</b> July 2008 to February 2011</p> <p><b>Follow-up until:</b> 5 years</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Myelodysplastic syndrome</li> <li>• IPSS low or intermediate-1</li> <li>• Platelet count <math>&lt; 20 \times 10^9/L</math> or platelet count <math>\geq 20 \times 10^9/L</math> with bleeding</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Disease modifying treatments or growth factors within 4 weeks of start of study</li> </ul> <p><b>Number of participants randomised:</b> 250</p> <p><b>Number of participants analysed:</b> 250</p> <p><b>Age:</b></p> <p>Intervention group: Median 71 years (interquartile range 62 to 77 years)</p> <p>Comparator group: Median 69 years (interquartile range 61 to 76 years)</p>

	<b>Gender:</b> Intervention group: Male 95 and Female 72 Comparator group: Male 53 and Female 30 <b>Types of malignancy:</b> All participants had myelodysplastic syndrome Intervention group: IPSS low: 40, intermediate-1: 120, intermediate-2: 1, unknown: 6 Control group: IPSS low: 23, intermediate-1: 58, unknown: 2 <b>Chemotherapy regimens:</b> Not receiving chemotherapy	
Interventions	<b>Intervention arm:</b> 750 µg romiplostim subcutaneously weekly for 26 weeks, then a 4 week washout. Participants could receive a further 24 weeks treatment as randomised after this, followed by a four week washout. N = 167 <b>Comparator arm:</b> Matching placebo subcutaneously weekly for 26 weeks, then a 4 week washout. Participants could receive a further 24 weeks treatment as randomised after this, followed by a four week washout. N = 83	
Outcomes	<b>Primary outcome:</b> <ul style="list-style-type: none"><li>● Clinically significant bleeding events (WHO grade 2+)</li></ul> <b>Secondary outcomes:</b> <ul style="list-style-type: none"><li>● Platelet transfusions</li><li>● Overall bleeding</li><li>● Platelet response</li><li>● Overall survival</li><li>● Progressive disease</li><li>● Antibodies to romiplostim or thrombopoietin</li></ul>	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Insufficient information for judgement
Allocation concealment (selection bias)	Low risk	“Randomization was facilitated through the interactive voice response system (IVRS)”
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information for judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information for judgement

Giagounidis 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants were included on an intention-to-treat basis but study was stopped early
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in protocol were reported
Other bias	High risk	Potentially at risk of bias because the authors have the following relationships with the trial sponsor <ul style="list-style-type: none"> <li>• Served on advisory boards</li> <li>• Received research funding</li> <li>• Received honoraria</li> <li>• Worked as consultants</li> <li>• Employees</li> <li>• Stockholders</li> </ul>

Greenberg 2013

Methods	<p><b>Type of study:</b> National, multi-centre, parallel groups two-arm, randomised controlled trial</p> <p><b>Countries where study was performed:</b> USA</p> <p><b>Dates of trial:</b> April 2008 to October 2009</p> <p><b>Follow-up until:</b> 16 weeks</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Age 18+ years</li> <li>• Myelodysplastic syndrome on bone marrow biopsy (WHO classification)</li> <li>• IPSS low, Int-1 or Int-2</li> <li>• Planned for at least 4 cycles decitabine</li> <li>• Eastern Cooperative Oncology Group performance status 0-2</li> <li>• Normal renal and liver function</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Previously received more than three cycles of decitabine, any hypomethylating agent within 30 days prior to screening, oprelvekin (interleukin-11 [IL-11], Neumega) or any experimental drug within 4 weeks of screening, or any other thrombopoietic growth factor</li> <li>• History of leukaemia, aplastic anaemia or bone marrow transplant</li> <li>• Prior malignancy (other than in situ cervical cancer, controlled prostate cancer or basal cell skin cancer) unless disease-free for 3 years before randomisation</li> <li>• Active or uncontrolled infections</li> <li>• Uncontrolled cardiovascular disease or a history of arterial thrombosis within 1 year of screening or venous thrombosis requiring anticoagulation therapy</li> </ul> <p><b>Number of participants randomised:</b> 29</p> <p><b>Number of participants analysed:</b> 29</p> <p><b>Age:</b></p> <p>Intervention group: Median 68 years (range 55 to 81 years)</p> <p>Comparator group: Median 72 years (range 58 to 84 years)</p>

	<b>Gender:</b> Intervention group: Male 8 and Female 7 Comparator group: Male 11 and Female 3 <b>Types of malignancy:</b> All participants had myelodysplastic syndrome Intervention group: IPSS low: 2, intermediate-1: 8, intermediate-2: 4, high: 1 Control group: IPSS low: 1, intermediate-1: 3, intermediate-2: 10 <b>Chemotherapy regimens:</b> Decitabine 15mg/m <sup>2</sup> intravenously over three hours repeated every eight hours for three days every six weeks; or a five-day dosing regimen (Dectiabine 20 mg/m <sup>2</sup> intravenously over one hour for five days every four weeks)	
Interventions	<b>Intervention arm:</b> 750 µg romiplostim subcutaneously weekly for up to four cycles of decitabine. N = 15 <b>Comparator arm:</b> Matching placebo subcutaneously weekly for up to four cycles of decitabine. N = 14	
Outcomes	<b>Primary outcome:</b> <ul style="list-style-type: none"><li>● Incidence of clinically significant thrombocytopenic events</li></ul> <b>Secondary outcomes:</b> <ul style="list-style-type: none"><li>● 1. Safety and tolerability of romiplostim</li><li>● 2. Proportion of participants receiving decitabine at recommended dose and schedule</li><li>● 3. Platelet transfusions</li><li>● 4. Clinical response</li><li>● 5. Bleeding</li><li>● 6. Progression to acute myeloid leukaemia</li></ul>	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Insufficient information for judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information for judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Placebo and romiplostim were provided in identical glass vials”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Placebo and romiplostim were provided in identical glass vials”
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the final analysis

Selective reporting (reporting bias)	Low risk	All data mentioned in protocol were reported.
Other bias	High risk	Potentially at risk of bias because the authors have the following relationships with the trial sponsor <ul style="list-style-type: none"> <li>• Received research funding</li> <li>• Worked as consultants</li> <li>• Employees</li> <li>• Stockholders</li> <li>• Received payment for writing the manuscript</li> </ul>

## Kantarjian 2010

Methods	<p><b>Type of study:</b> National, multi-centre, parallel groups three-arm, randomised controlled trial</p> <p><b>Countries where study was performed:</b> USA</p> <p><b>Dates of trial:</b> Not reported</p> <p><b>Follow-up until:</b> 16 weeks</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Patients 18 years of age or older</li> <li>• Myelodysplastic syndrome diagnosed by bone marrow biopsy based on the World Health Organization (WHO) classification were eligible if they had IPSS low, intermediate-1, or intermediate-2 risk disease, and were to be treated with azacitidine for at least 4 cycles</li> <li>• Eastern Cooperative Oncology Group performance status 0 to 2</li> <li>• Adequate liver function and serum creatinine</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• More than 3 previous cycles of azacitidine or any hypomethylating agent within 30 days</li> <li>• History of leukaemia, aplastic anaemia, or bone marrow transplantation or prior malignancy unless treated with curative intent and without disease evidence</li> <li>• For 3 years</li> <li>• Active infection</li> <li>• Uncontrolled cardiovascular disease</li> <li>• Recent myocardial infarction or arterial thrombosis</li> <li>• History of venous thrombosis or current use of anticoagulation therapy</li> <li>• Interleukin-11 or any experimental drug or device within 4 weeks of screening or previously received another thrombopoietic growth factor</li> </ul> <p><b>Number of participants randomised:</b> 40</p> <p><b>Number of participants analysed:</b> 40</p> <p><b>Age:</b></p> <p>Intervention group 1: Median 72 years (range 56 to 86 years)</p> <p>Intervention group 2: Median 72 years (range 61 to 81 years)</p> <p>Comparator group: Median 64 years (range 58 to 86 years)</p>



	<p><b>Gender:</b> Intervention group 1: Male 7 and Female 6 Intervention group 2: Male 7 and Female 7 Comparator group: Male 7 and Female 6</p> <p><b>Types of malignancy:</b> All participants had myelodysplastic syndrome Intervention group 1: IPSS low: 1, intermediate-1: 9, intermediate-2: 3 Intervention group 2: IPSS low: 1, intermediate-1: 9, intermediate-2: 4 Control group: IPSS low: 1, intermediate-1: 5, intermediate-2: 7</p> <p><b>Chemotherapy regimens:</b> Azacitidine 75 mg/m<sup>2</sup> subcutaneously daily for the first 7 days of each 28-day cycle (up to four cycles)</p>	
Interventions	<p><b>Intervention arm 1:</b> 500 µg romiplostim subcutaneously weekly for four cycles of azacitidine. N = 13</p> <p><b>Intervention arm 2:</b> 750 µg romiplostim subcutaneously weekly for four cycles of azacitidine. N = 14</p> <p><b>Comparator arm:</b> Matching placebo subcutaneously weekly for four cycles of azacitidine. N = 13</p>	
Outcomes	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"><li>● Incidence of clinically significant thrombocytopenic events</li></ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"><li>● 1. Safety and tolerability of romiplostim</li><li>● 2. Proportion of participants receiving decitabine at recommended dose and schedule</li><li>● 3. Platelet transfusions</li><li>● 4. Clinical response</li><li>● 5. Bleeding</li><li>● 6. Progression to acute myeloid leukaemia</li></ul>	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Insufficient information for judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information for judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information for judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information for judgement

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the final analysis
Selective reporting (reporting bias)	Low risk	All data mentioned in protocol were reported.
Other bias	High risk	Potentially at risk of bias because the authors have the following relationships with the trial sponsor <ul style="list-style-type: none"> <li>• Received research funding</li> <li>• Worked as consultants</li> <li>• Employees</li> <li>• Stockholders</li> </ul>

## Mannucci 1986

Methods	<b>Type of study:</b> Multi-national, multi-centre, two-,arm, cross-over randomised controlled trial <b>Countries where study was performed:</b> Italy and Spain <b>Dates of trial:</b> Not reported <b>Follow-up until:</b> 4 hours
Participants	<b>Inclusions:</b> Bleeding time more than 10 minutes <b>Exclusions:</b> No exclusions stated <b>Number of participants randomised:</b> 53 (8 with chronic bone marrow failure) <b>Number of participants analysed:</b> 53 (8 with chronic bone marrow failure) <b>Age:</b> Not reported for subgroup with bone marrow failure <b>Gender:</b> Not reported for subgroup with bone marrow failure <b>Types of malignancy:</b> Aplastic anaemia: 7, familial thrombocytopenia: 1 <b>Chemotherapy regimens:</b> Not reported
Interventions	<b>Intervention arm:</b> Single intravenous infusion of 0.3µg/kg DDAVP in 50 mL 0.9% saline over 30 minutes <b>Comparator arm:</b> Single intravenous infusion of placebo (50 mL 0.9% saline) over 30 minutes
Outcomes	<b>Primary outcome:</b> Bleeding time <b>Secondary outcomes:</b> None stated
Notes	Additional information provided by Professor Mannucci on 18th June 2016

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unpublished information: the randomisation was made by means of sealed envelopes with a block size of two and the sequence of treatments was computer-generated
Allocation concealment (selection bias)	Low risk	Unpublished information: the randomisation was made by means of sealed envelopes with a block size of two and the sequence of treatments was computer-generated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adequate blinding of all participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adequate blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in final analysis
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	DDAVP acts by increasing von Willebrand factor (vWF) levels. For all participants, vWF levels were 2-3 times the expected level at baseline which may have reduced the effect of DDAVP. It is unclear if the difference in baseline vWF levels will have reduced the efficacy of DDAVP

## Platzbecker 2015

Methods	<p><b>Type of study:</b> Multi-national, multi-centre, parallel groups, two-arm, randomised controlled trial</p> <p><b>Countries where study was performed:</b> Brazil, Denmark, France, Germany, Hong Kong, Italy, South Korea, Taiwan, UK and USA</p> <p><b>Dates of trial:</b> May 2009 to May 2013</p> <p><b>Follow-up until:</b> 12 months</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Myelodysplastic syndrome or acute myeloid leukaemia</li> <li>• Platelet count &lt; 30 within 4 weeks of randomisation or those who were platelet dependent (two or more platelet transfusions in the four weeks before randomisation).</li> </ul>

	<ul style="list-style-type: none"><li>● Patients with stable disease (peripheral blasts over time not suggestive of highly proliferative disease)</li></ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"><li>● Pre-existing cardiovascular disease</li><li>● Cardiac arrhythmia known to increase risk of thromboembolic events</li><li>● Liver cirrhosis</li><li>● Active and uncontrolled infections</li><li>● Hepatitis B, C or HIV</li></ul> <p><b>Number of participants randomised:</b> 98</p> <p><b>Number of participants analysed:</b> 98</p> <p><b>Age:</b></p> <p>Intervention group: Median 73 years (range 29 to 88 years)</p> <p>Comparator group: Median 71 years (range 40 to 91 years)</p> <p><b>Gender:</b></p> <p>Intervention group: Male 34 and Female 30</p> <p>Comparator group: Male 25 and Female 9</p> <p><b>Types of malignancy:</b></p> <p>Intervention group: Myelodysplastic syndrome refractory anaemia with excess blasts-2: 15, acute myeloid leukaemia: 48, unknown: 1</p> <p>Control group: Myelodysplastic syndrome refractory anaemia with excess blasts-2: 11, acute myeloid leukaemia: 22, unknown: 1</p> <p><b>Chemotherapy regimens:</b></p> <p>Not receiving chemotherapy</p>	
Interventions	<p><b>Intervention arm:</b></p> <p>Eltrombopag 50 mg once daily which was increased every 2 weeks based on the patients’s platelet and peripheral bone marrow blast counts (doses of 100, 200 and 300mg, or 100 and 150mg for patients of East Asian heritage who have a different pharmacokinetic profile to individuals of other ethnic origins examined). Continued for 6 months then an optional continuation phase of six months N = 64</p> <p><b>Comparator arm:</b></p> <p>Matching oral placebo daily for 6 months then an optional continuation phase of six months. N = 34</p>	
Outcomes	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"><li>● Safety and tolerability of eltrombopag</li></ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"><li>● Proportion of participants with a platelet response</li><li>● Platelet transfusions</li><li>● Duration of platelet independence</li><li>● Overall survival</li><li>● Plasma eltrombopag concentration</li></ul>	
Notes		
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	“Patients were randomly assigned (2:1), according to a permuted block randomisation schedule (block sizes of three), to receive either eltrombopag or matching placebo”
Allocation concealment (selection bias)	Low risk	“Randomisation of patients and allocation of study drugs was done with the GlaxoSmithKline Registration and Medication Ordering System, a telephone-based interactive voice-response system”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Patients, study investigators and the study sponsor were masked to treatment allocation”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Patients, study investigators and the study sponsor were masked to treatment allocation”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was by intention-to-treat and all participants were included in the final analysis
Selective reporting (reporting bias)	High risk	No reporting of quality of life despite mentioned in clinical trial protocol
Other bias	High risk	Potentially at risk of bias because the authors have the following relationships with the trial sponsor <ul style="list-style-type: none"> <li>• Served on advisory boards</li> <li>• Received research funding</li> <li>• Received honoraria</li> <li>• Worked as consultants</li> <li>• Employees</li> <li>• Stockholder</li> </ul>

## Wang 2012

Methods	<p><b>Type of study:</b> National, multi-centre, parallel groups three-arm, randomised controlled trial</p> <p><b>Countries where study was performed:</b> USA</p> <p><b>Dates of trial:</b> March 2007 to March 2009</p> <p><b>Follow-up until:</b> 16 weeks</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Adult patients</li> <li>• Myelodysplastic syndrome based on World Health Organization (WHO) 2001</li> </ul>

	<p>classification of marrow findings with IPSS lower-risk myelodysplastic syndrome disease</p> <ul style="list-style-type: none"> <li>• Eastern Cooperative Oncology Group performance status of 0-2</li> <li>• Adequate liver and kidney function</li> <li>• All patients agreed to receive <math>\geq 4</math> cycles of lenalidomide capsules 10 mg by mouth daily.</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Previous exposure to <math>&gt; 3</math> cycles of lenalidomide or exposure to lenalidomide within the last 30 days</li> <li>• History of leukaemia or aplastic anaemia, stem cell transplantation, or prior malignancy (other than in situ cervical cancer or basal cell cancer of the skin) unless treated with curative intent and without evidence of disease for <math>\geq 3</math> years before randomisation</li> <li>• Active or uncontrolled infections</li> <li>• Uncontrolled cardiovascular disease</li> <li>• History of arterial or venous thrombosis within the past year</li> <li>• IL-11 within 4 weeks of screening</li> <li>• Any investigational drug or device <math>&lt; 4</math> weeks previously</li> <li>• Any other thrombopoietic growth factor.</li> </ul> <p><b>Number of participants randomised:</b> 39</p> <p><b>Number of participants analysed:</b> 39</p> <p><b>Age:</b></p> <p>Intervention group 1: Median 75 years (range 49 to 90 years)</p> <p>Intervention group 2: Median 65 years (range 49 to 83 years)</p> <p>Comparator group: Median 79 years (range 39 to 87 years)</p> <p><b>Gender:</b></p> <p>Intervention group 1: Male 8 and Female 6</p> <p>Intervention group 1: Male 8 and Female 5</p> <p>Comparator group: Male 8 and Female 4</p> <p><b>Types of malignancy:</b></p> <p>All participants had myelodysplastic syndrome</p> <p>Intervention group 1: IPSS low: 4, intermediate-1: 8, intermediate-2: 1, unknown: 1</p> <p>Intervention group 2: IPSS low: 6, intermediate-1: 7</p> <p>Control group: IPSS low: 4, intermediate-1: 6, intermediate-2: 1, unknown: 1</p> <p><b>Chemotherapy regimens:</b></p> <p>Lenalidomide 10mg orally daily for 16 weeks</p>
Interventions	<p><b>Intervention arm 1:</b></p> <p>500 <math>\mu</math>g romiplostim subcutaneously weekly for 16 weeks. N = 14</p> <p><b>Intervention arm 2:</b></p> <p>750 <math>\mu</math>g romiplostim subcutaneously weekly for 16 weeks. N = 13</p> <p><b>Comparator arm:</b></p> <p>Matching placebo subcutaneously weekly for 16 weeks. N = 12</p>
Outcomes	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>• Safety and tolerability of romiplostim</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Clinically significant platelet transfusion events</li> <li>• Number of participants who continued lenalidomide at the original dose and</li> </ul>

	timings <ul style="list-style-type: none"> <li>• Platelet transfusions</li> <li>• Disease response</li> <li>• Bleeding events</li> <li>• Formation of antibodies that cross-reacted with endogenous thrombopoietin</li> </ul>	
Notes		
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Insufficient information for judgement
Allocation concealment (selection bias)	Low risk	"Patients were assigned identification numbers from an interactive voice response system (IVRS) and randomly assigned in a 1:1:1 ratio to receive placebo or romiplostim 500 µg or 750 µg"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	During the double-blind portion of the study, investigational product was packaged in two identical vials for each scheduled dose for each patient. Patients received 1.5 mL of investigational product in each dose-1 mL from one vial and 0.5 mL from the second vial. Patients in the 500 µg group received 1 mL of romiplostim and 0.5 mL of placebo, patients in the 750 µg group received 1.5 mL of romiplostim, and patients in the placebo group received 1.5 mL of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	During the double-blind portion of the study, investigational product was packaged in two identical vials for each scheduled dose for each patient. Patients received 1.5 mL of investigational product in each dose - 1 mL from one vial and 0.5 mL from the second vial. Patients in the 500 µg group received 1 mL of romiplostim and 0.5 mL of placebo, patients in the 750 µg group received 1.5 mL of romiplostim, and patients in the placebo group received 1.5 mL of placebo

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in the final analyses. Two participants found not to meet inclusion criteria after randomisation but were included in intention to treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes from trial protocol included in final report
Other bias	High risk	Potentially at risk of bias because the authors have the following relationships with the trial sponsor <ul style="list-style-type: none"> <li>• Worked on advisory boards</li> <li>• Received research funding</li> <li>• Received honoraria</li> <li>• Worked as consultants</li> <li>• Employees</li> <li>• Stockholders</li> </ul>

IPSS: International Prognostic Scoring System

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
<a href="#">ACTRN12610000641099</a>	Not a randomised controlled trial
<a href="#">Antun 2013</a>	Not a randomised controlled trial
<a href="#">Archimbaud 1999</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">Bussel 2007</a>	Wrong participant group
<a href="#">Castamann 1997</a>	Not a randomised controlled trial
<a href="#">Cattan 1963</a>	Not a randomised controlled trial
<a href="#">Chen 2010</a>	Wrong participant group
<a href="#">Desmond 2014</a>	Not a randomised controlled trial
<a href="#">Dickinson 2014</a>	Not a randomised controlled trial



(Continued)

<a href="#">EudraCT 2012-004886-42</a>	Not a randomised controlled trial
<a href="#">Fenaux 2013</a>	Not a randomised controlled trial
<a href="#">Geissler 2003</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">Gerrits 2015</a>	Not a randomised controlled trial
<a href="#">Giles 2005</a>	Wrong participant group
<a href="#">Gordon 1995</a>	Not a randomised controlled trial
<a href="#">Han 2015</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">Higby 1974</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">ISRCTN73545489</a>	Wrong participant group
<a href="#">Kantarjian 2007</a>	Not a randomised controlled trial
<a href="#">Kantarjian 2012</a>	Not a randomised controlled trial
<a href="#">Khan 2015</a>	Incorrect intervention
<a href="#">Kurzrock 2001</a>	Not a randomised controlled trial
<a href="#">Miao 2012</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">Mittelman 2012</a>	Not a randomised controlled trial
<a href="#">Montero 2006</a>	Not a randomised controlled trial
<a href="#">Moskowitz 2007</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">NCT01286038</a>	Not a randomised controlled trial
<a href="#">NCT01481220</a>	Not a randomised controlled trial
<a href="#">NCT01893372</a>	Incorrect intervention

(Continued)

<a href="#">NCT02094248</a>	Wrong participant group
<a href="#">NCT02094417</a>	Incorrect intervention
<a href="#">NCT02578901</a>	Wrong participant group
<a href="#">NIHR 2014</a>	Review article
<a href="#">Olnes 2012</a>	Not a randomised controlled trial
<a href="#">Pecci 2010</a>	Not a randomised controlled trial
<a href="#">Perez Ruixo 2012</a>	Not a randomised controlled trial
<a href="#">Ramadan 2015</a>	Not a randomised controlled trial
<a href="#">Reynolds 2000</a>	Review article
<a href="#">Schiffer 2000</a>	Wrong participant group. Included in review of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation ( <a href="#">Desborough 2016b</a> )
<a href="#">Schrezenmeier 1995</a>	Not a randomised controlled trial
<a href="#">Sekeres 2009</a>	Not a randomised controlled trial
<a href="#">Svensson 2014</a>	Not a randomised controlled trial
<a href="#">Usuki 2007</a>	Wrong participant group
<a href="#">Will 2009</a>	Not a randomised controlled trial
<a href="#">Young 1997</a>	Not a randomised controlled trial

## Characteristics of ongoing studies [ordered by study ID]

### [EudraCT 2010-022890-33](#)

Trial name or title	Eltrombopag for the treatment of thrombocytopenia due to low- and intermediate risk myelodysplastic syndromes
Methods	<b>Type of study:</b> Multi-national, multi-centre parallel groups two-arm randomised controlled trial <b>Countries where study is being performed:</b> France, Germany, Italy and USA <b>Follow-up:</b> 6 months

Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Adult participants (18 years of age or older)</li> <li>• Low or intermediate-1 IPSS risk MDS and stable disease</li> <li>• Platelet count taken within the 4 weeks prior to randomisation that is <math>&lt; 30 \times 10^9/L</math></li> <li>• Ineligible or relapsed or refractory to receive other treatment options (such as azacitidine) and must be ineligible to receive intensive chemotherapy or autologous/allogeneic stem cell transplantation</li> <li>• Platelet count and platelet transfusion data available over a period of 8 weeks prior to randomisation</li> <li>• During the 2 months prior to randomisation, participants must have a baseline BM examination which includes cytomorphology and cytogenetics. Histopathology should be performed</li> <li>• Erythropoiesis-stimulating agents (ESAs) in anaemic participants or granulocyte colony stimulating factor (G-CSF) in participants with severe neutropenia and recurrent infections are allowed during the study as per accepted standards. Participants who enter the study on ESAs or G-CSF should continue at the same dose schedule until the optimal dose of study medication has been established</li> <li>• ECOG Performance Status 0-3</li> <li>• Able to understand and comply with protocol requirements and instructions</li> <li>• Signed and dated informed consent</li> <li>• Adequate baseline organ function defined by the criteria below: total bilirubin (except for Gilbert's Syndrome) <math>\leq 1.5 \times</math> upper limit of normal (ULN) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <math>\leq 3 \times</math> ULN creatinine <math>\leq 2 \times</math> ULN albumin must not be below the lower limit of normal by more than 20%</li> <li>• Practicing an acceptable method of contraception. Female participants (or female partners of male participants) must either be of non-childbearing potential (hysterectomy, bilateral oophorectomy, bilateral tubal ligation or post-menopausal <math>&gt;1</math> year), or of childbearing potential and use of an highly effective method of contraception from 2 weeks prior to administration of study medication, throughout the study, and 28 days after completion or premature discontinuation from the study</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• MDS with intermediate-2 or high IPSS risk</li> <li>• History of treatment for cancer other than MDS or sAML/MDS with systemic chemotherapy and/or radiotherapy within the last 2 years</li> <li>• History of treatment with romiplostim or other TPO-R agonists</li> <li>• Pre-existing cardiovascular disease (including congestive heart failure, New York Heart Association [NYHA] Grade III/IV), or arrhythmia known to increase the risk of thromboembolic events (e.g. persistent atrial fibrillation), or participants with a QTc <math>&gt; 450</math> msec (QTc <math>&gt; 480</math> msec for participants with Bundle Branch Block)</li> <li>• BM fibrosis that leads to an inability to aspirate marrow for assessment</li> <li>• Spleen size <math>&gt; 14</math> cm (length as per ultrasound examination)</li> <li>• Leukocytosis <math>\geq 25 \times 10^9/L</math> prior to Day 1 of study medication</li> <li>• Female participants who are nursing or pregnant (positive serum or urine Beta-human chorionic gonadotropin [B-hCG] pregnancy test) at screening or pre-dose on Day 1</li> <li>• Current alcohol or drug abuse</li> <li>• Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication</li> <li>• Active and uncontrolled infections</li> <li>• Participants infected with Hepatitis B, C or Human Immunodeficiency Virus (HIV)</li> </ul>
Interventions	<p><b>Intervention arm:</b> Eltrombopag 50 mg/day orally for 6 months</p> <p><b>Comparator arm:</b> Placebo once daily orally for 6 months</p>

Outcomes	<p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Response rate: The proportion of patients achieving a complete response (CR) or response (R) during the six month treatment period, for participants receiving eltrombopag relative to placebo</li> <li>• Safety and tolerability in terms of frequency of adverse events (AE)s and serious adverse events (SAE), for participants receiving eltrombopag relative to placebo.</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Quality of life (QoL) scores for participants receiving eltrombopag relative to placebo</li> <li>• The number of monthly platelet transfusions in participants receiving eltrombopag compared to the placebo group</li> <li>• The duration of transfusion independence as measured in weeks and months for participants receiving eltrombopag relative to placebo</li> <li>• Time to response (time from starting treatment to time of achievement of CR or PR) between treatment groups as measured by the MDS response criteria</li> <li>• The incidence and severity of bleeding using the WHO Bleeding Scale for participants receiving eltrombopag relative to placebo</li> <li>• Overall survival (OS) at 2 years. Event for OS in both arms is death and patients are censored at the date of last contact if alive</li> <li>• Leukemia-free survival (LFS) at 2 years. Events for LFS in both arms are death and progression to acute myeloid leukaemia</li> <li>• To evaluate eltrombopag population pharmacokinetics</li> </ul>
Starting date	November 2010
Contact information	<b>Principal Investigator:</b> Esther Natalie Oliva (qolone@gmail.com)
Notes	<p><b>Expected number of participants:</b> 171</p> <p><b>Expected completion date:</b> Not reported. New sites opened in June 2014 and at least five years of follow-up planned. Earliest possible date for completion would be June 2019</p>

## EudraCT 2014-000174-19

Trial name or title	Efficacy and safety of eltrombopag in patients with acquired moderate aplastic anemia (EMAA) who are treated with ciclosporin A
Methods	<p><b>Type of study:</b> Multi-national, multi-centre parallel groups two arm-randomised controlled trial</p> <p><b>Countries where study is being performed:</b> France, Germany, Italy, the Netherlands, Switzerland, UK</p> <p><b>Follow-up:</b> 6 months</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Moderate aplastic anaemia (MAA): defined as aplastic anaemia fulfilling the following criteria: No evidence for other disease causing marrow failure; hypocellular bone marrow for age; and depression of at least two out of three peripheral blood counts below the normal values: absolute neutrophil count (ANC) &lt; <math>1.2 \times 10^9/L</math>, platelet count &lt; <math>70 \times 10^9/L</math>, absolute reticulocyte count &lt; <math>60 \times 10^9/L</math>, without fulfilling the criteria for SAA</li> <li>• Platelet transfusion dependency is defined as prophylactic transfusion (platelet counts &lt; <math>10 \times 10^9/L</math> with no bleeding) or therapeutic transfusion</li> <li>• Red cell transfusion dependency is defined as transfusion of at least 4 units of packed red blood cell concentrates (PRBC) in the 12 weeks prior to study entry</li> </ul>

	<ul style="list-style-type: none"> <li>• A signed and dated informed consent.</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Age &lt; 18 years</li> <li>• Severe or very severe aplastic anaemia (hypocellularity of bone marrow 25% and depression of two of the three peripheral counts: ANC &lt; <math>0.5 \times 10^9/L</math>, platelet count &lt; <math>20 \times 10^9/L</math>, reticulocyte count &lt; <math>20 \times 10^9/L</math>)</li> <li>• Diagnosis of Fanconi anaemia</li> <li>• Clonal myeloid disorders based on cytogenetic findings performed within 12 weeks of study entry. Especially patients with cytogenetic abnormalities which are recurrent in MDS are not eligible for the study</li> <li>• Bone marrow reticulin fibrosis of grade 3 or greater</li> <li>• Severe concurrent diseases precluding the patient's ability to tolerate protocol therapy</li> <li>• ALT &gt; 3 times the upper limit of normal if this elevation is progressive, or persistent for 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation</li> <li>• Infection not adequately responding to appropriate therapy</li> <li>• HIV-positivity, patients with Hepatitis B or Hepatitis C are only in combination with hepatic failure excluded</li> <li>• Moribund status with a likely death within 3 months</li> <li>• History of malignancy other than localized tumours diagnosed more than one year previously and treated surgically with curative intent (for instance squamous cell or other skin cancers, stage 1, breast cancer or cervical carcinoma in situ). <ul style="list-style-type: none"> <li>• Prior specific treatment of aplastic anaemia with immunosuppression or androgens or interleukin2-receptorantibodies. The use of these drugs in context of other disorders before diagnosis of aplastic anaemia is not an exclusion criteria if these treatments were finished longer than 6 months before study entry.</li> <li>• Treatment with other haematological effective drugs (including growth factors) within 3 months before study entry as well as treatment with corticosteroids within 3 weeks before enrolment</li> <li>• Known hypersensitivity to eltrombopag or its components</li> <li>• Current nursing, pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control to refrain from pregnancy as well as a missing or positive pregnancy test within the last 14 days before inclusion for women of childbearing potential during the course of this study</li> <li>• Inability to understand the investigational nature of the study or to give informed consent.</li> <li>• Renal failure with creatinine &gt; 2 x upper limit of normal.</li> </ul> </li> </ul>
Interventions	<p><b>Intervention arm:</b> Eltrombopag 75 mg/day orally for 6 months</p> <p><b>Comparator arm:</b> Placebo once daily orally for 6 months</p>
Outcomes	<p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Haematologic response (PR and CR) at 6 months</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Trilineage haematological response rate (CR and PR) at 3, 6, 12 and 18 months</li> <li>• Single lineage response at 3, 6, 12 and 18 months</li> <li>• Cumulative incidence of response</li> <li>• Time to best haematological and single lineage response</li> <li>• Proportion of patients with need for transfusions and number of units transfused (PRBC and PC) since start of treatment</li> <li>• Cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG</li> <li>• Toxicity profile as measured using the CTCAE criteria for patients receiving placebo in comparison to</li> </ul>

	<p>patients receiving eltrombopag, both on top of background treatment with CSA</p> <ul style="list-style-type: none"> <li>● Relapse rate at 6, 12 and 18 months</li> <li>● Cumulative incidence of relapse (from best haematological response)</li> <li>● Overall survival</li> <li>● Failure-free survival</li> <li>● Telomere lengths and presence of telomerase mutations as biomarkers for response</li> <li>● Quality of life as assessed by quality of life instruments (FACIT-F SCALE and EORTC QLQ-C30, partly in addition with the QLQ-AA/PNH)N</li> </ul>
Starting date	January 2015
Contact information	<b>Principal Investigator:</b> Britta Höchsmann (Email: b.hoechsmann@blutspende.de)
Notes	<p><b>Expected number of participants:</b> 116</p> <p><b>Expected completion date:</b> Not reported</p>

## NCT02099747

Trial name or title	A prospective randomized multicenter study comparing horse antithymocyte globuline (hATG) + cyclosporine A (CsA) with or without eltrombopag as front-line therapy for severe aplastic anemia patients
Methods	<p><b>Type of study:</b> Multi-national, multi-centre parallel groups two-arm randomised controlled trial</p> <p><b>Countries where study is being performed:</b> France, Germany, Italy, the Netherlands and Switzerland</p> <p><b>Follow-up:</b> 2 years</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>● Diagnosis of severe or very severe aplastic anaemia, defined by: At least two of the following: absolute neutrophil counts <math>&lt; 0.5 \times 10^9/L</math> (severe) or <math>&lt; 0.2 \times 10^9/L</math> (very severe), platelet counts <math>&lt; 20 \times 10^9/L</math>, reticulocyte counts <math>&lt; 60 \times 10^9/L</math>, hypocellular bone marrow (<math>&lt; 30\%</math> cellularity), without evidences of fibrosis or malignant cells</li> <li>● Age <math>&gt; 14</math> years</li> <li>● Written informed consent</li> <li>● Willing and able to comply with all of the requirements and visits in the protocol</li> <li>● Understands that they can be randomised to either treatment arm</li> <li>● Negative pregnancy test for women of child bearing age</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>● Prior immunosuppressive therapy with ATG (horse of rabbit) or any other lymphocyte depleting agent (i.e. alemtuzumab)</li> <li>● Eligibility to a sibling allogeneic stem cell transplantation</li> <li>● Evidence of a MDS, defined by the presence of myelodysplastic features, excess of blasts or karyotypic abnormalities typical of MDS (according to revised WHO 2008 criteria), as well as other primitive marrow disease. Patients with diagnosis of AA with cytogenetic abnormalities which are recurrent in MDS (according to revised WHO 2008 criteria) should be included in this category, and are not eligible for the study; patients with del(20q), +8 and -Y are not included in this category, and thus are eligible for this study</li> <li>● History or clinical suspect of constitutional aplastic anaemia (i.e. Fanconi anaemia with positive DEB/MMC test or Dyskeratosis Congenita)</li> <li>● History of malignant tumours with active disease within 5 years from enrolment, and/or previous chemo-radiotherapy</li> </ul>

	<ul style="list-style-type: none"> <li>• Previous history of stem cell transplantation treatment with cyclosporin A &lt;2 weeks before enrolment.</li> </ul> <p>Treatment with G-CSF &lt; 2 weeks before enrolment</p> <ul style="list-style-type: none"> <li>• CMV viraemia, as defined by positive PCR or pp65 test</li> <li>• WHO performance status <math>\geq 3</math></li> <li>• Pregnant or breast feeding patients</li> <li>• Patients with hepatic, renal or cardiac failure, or any other life- threatening concurrent disease</li> <li>• Patients with HIV infection</li> <li>• Patients without social health care assistance</li> <li>• Patients for whom there is no availability of horse-ATG (ATGAM)</li> <li>• Participation in another clinical trial within 1 month before the start of this trial</li> <li>• Patients and/or female partners of male patients not using highly effective method of birth control i.e. intrauterine device (IUD), hormonal (oral pill, injection, implants), tubal ligation or partner's vasectomy</li> </ul> <p>participants with known hypersensitivity to any of the component medications</p>
Interventions	<p><b>Intervention arm:</b> Eltrombopag 150 mg/day orally for 3 months</p> <p><b>Comparator arm:</b> Placebo once daily orally for 3 months</p>
Outcomes	<p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>• Complete response rate at three months</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Time to best haematological response</li> <li>• Haematological response at 6, 12, 18 and 24 months</li> <li>• Cumulative incidence of response</li> <li>• Overall survival</li> <li>• Event-free survival</li> <li>• Cumulative incidence of relapse rate</li> <li>• Cumulative incidences of clonal evolution</li> <li>• Cumulative incidence of paroxysmal nocturnal haemoglobinuria (PNH) population occurrence and clinical haemolytic PNH occurrence</li> <li>• Cumulative incidence of discontinuation of immunosuppressive therapy</li> <li>• Rate of ciclosporin A-independent haematological response</li> <li>• Need for transfusions and number of transfusions required from treatment</li> <li>• Need for any supportive care</li> <li>• Comparison of number of SAEs between the two arms</li> </ul>
Starting date	May 2015
Contact information	<p>Alain Barrois (Phone +31 71526 ext 5005; Email: alain.barrois@ebmt.org)</p> <p>Marleen van Os (Phone: +31 71526 ext 1988; Email: marlene.van_os_fransen@ebmt.org)</p>
Notes	<p><b>Expected number of participants:</b> 200</p> <p><b>Expected completion date:</b> December 2020</p>

Trial name or title	A study of eltrombopag or placebo in combination with azacitidine in subjects with international prognostic scoring system (IPSS) intermediate-1, intermediate-2 or high-risk myelodysplastic syndromes (MDS)
Methods	<p><b>Type of study:</b> Multi-national, multi-centre parallel groups two-arm randomised controlled trial</p> <p><b>Countries where study is being performed:</b> Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Norway, Peru, Poland, Puerto Rico, Russia, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey and USA</p> <p><b>Follow-up:</b> 5.5 years</p>
Participants	<p><b>Inclusions:</b></p> <ul style="list-style-type: none"> <li>• Age <math>\geq 18</math> years (For participants in Taiwan, Age <math>\geq 20</math> years)</li> <li>• MDS by World Health Organization (WHO) or French-American-British (FAB) classification Intermediate 1, intermediate 2 or high risk MDS by IPSS</li> <li>• At least one platelet count <math>&lt; 75 \times 10^9/L</math></li> <li>• Eastern Cooperative Oncology Group (ECOG) Status 0-2</li> <li>• Adequate baseline organ function defined by the criteria below: total bilirubin <math>\leq 1.5 \times</math> the upper limit of normal (ULN) except for Gilbert's syndrome or cases clearly not indicative of inadequate liver function (i.e. elevation of indirect [haemolytic] bilirubin in the absence of alanine aminotransferase [ALT] abnormality); ALT <math>\leq 2.5 \times</math> ULN; creatinine <math>\leq 2.5 \times</math> ULN</li> <li>• Participants with a corrected QT interval (QTc) <math>&lt; 450</math> milliseconds (msec) or <math>&lt; 480</math> msec for participants with bundle branch block. The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), machine or manual overread. For participant eligibility and withdrawal, QTcF will be used. For purposes of data analysis, QTcF will be used. The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period</li> <li>• Participant is able to understand and comply with protocol requirements and instructions</li> <li>• Participant has signed and dated informed consent</li> <li>• Women must be either of non-child bearing potential, or women with child-bearing potential and men with reproductive potential must be willing to practice acceptable methods of birth control during the study</li> <li>• Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception during the study and for 3 months following the last dose of study treatment</li> <li>• Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception from time of randomisation until 16 weeks after the last dose of study treatment</li> <li>• French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Previous treatment with hypomethylating agent or induction chemotherapy for MDS</li> <li>• Proliferative type chronic myelomonocytic leukaemia with white blood cell count <math>&gt; 12 \times 10^9/L</math> at any time during the 28 days before Day 1</li> <li>• History of treatment with eltrombopag, romiplostim or other thrombopoietin receptor (TPO-R) agonists</li> <li>• Previous allogeneic stem-cell transplantation</li> <li>• Known thrombophilic risk factors. Exception: participants for whom the potential benefits of participating in the study outweigh the potential risks of thromboembolic events, as determined by the investigator</li> <li>• Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of investigational product (eltrombopag/placebo)</li> <li>• Active and uncontrolled infections, including hepatitis B or C</li> <li>• Human Immunodeficiency Virus (HIV) infection</li> </ul>



	<ul style="list-style-type: none"> <li>• Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to eltrombopag or its excipient, or azacitidine, that contraindicates the participant's participation</li> <li>• Pregnant or lactating female</li> <li>• Any serious and/or unstable pre-existing medical condition (including any advanced malignancy other than the disease under study), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance with the study procedures</li> <li>• French participants: the French participant has participated in any study using an investigational drug during the previous 30 days</li> </ul>
Interventions	<p><b>Intervention arm:</b> Eltrombopag 200 mg daily (100 mg for participants of East Asian heritage). Dose modifications of eltrombopag will be permitted by 100 mg increments (50 mg increments for East Asians) to a lowest dose of 100 mg (50 mg for East Asian heritage) or a maximum dose of 300 mg (150 mg for East Asian heritage) in order to maintain platelet counts at a safe and effective level (i.e. a level sufficient to avoid platelet transfusions and bleeding events). Treatment will continue for the duration of up to 4 cycles of azacitidine therapy</p> <p><b>Comparator arm:</b> Placebo once daily orally for the duration of up to 4 cycles of azacitidine therapy</p>
Outcomes	<p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• The proportion of participants who are platelet transfusion-free during Cycles 1-4 of azacitidine therapy. A participant is defined as being platelet transfusion independent if they receive no platelet transfusions within the first 4 cycles of treatment with azacitidine</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Overall survival is defined as the time from randomisation until death due to any cause. Participants still alive at the time of the analysis and participants who have withdrawn from the study will be censored at the time of last contact</li> <li>• Best disease response categorised as complete remission (CR), partial remission (PR), or marrow CR, stable disease, disease progression, and as non-evaluable; according to modified 2006 International Working Group (IWG) criteria for MDS</li> <li>• Duration of disease response will be summarized for participants who had some form of response</li> <li>• Progression-free survival is defined as the time from randomisation until either disease progression or death</li> <li>• Time to progression defined as the time from patient inclusion to the date of the first documented date of disease progression (using the modified 2006 IWG response criteria for MDS)</li> <li>• Time to progression defined as the time from patient inclusion to the date of the first documented date of acute myeloid leukaemia progression (defined as meeting the definition of disease progression)</li> <li>• Haematologic improvement (HI) in platelets, neutrophils, and haemoglobin calculated based on the modified IWG criteria for MDS</li> <li>• Duration of HI will be summarised for participants who had some form of response</li> <li>• Number of platelet and Red Blood Cells (RBC) transfusions</li> <li>• Duration of platelet and RBC transfusion-independence is defined as a time period where participants do not receive any platelet or RBC transfusions during the treatment period and follow-up</li> <li>• Bleeding adverse events (AEs) <math>\geq</math> CTCAE Grade 3</li> <li>• The proportion of participants with any delay or reduction in dosage of azacitidine excluding those for non-medical reasons will be analysed</li> <li>• Evaluation of adverse event reporting</li> <li>• Changes from baseline in all domains of Euroqol-5 Dimensions of Health, 3 Response Levels (EQ-5D-3L™)</li> <li>• Changes from baseline in all domains of Functional Assessment of Chronic Disease Therapy-fatigue</li> </ul>

	subscale (FACIT-Fatigue) <ul style="list-style-type: none"> <li>• Changes from baseline in all domains of European Organization for Research and Treatment of Cancer - Quality of Life questionnaire - 30 item (EORTC QLQ-C30)</li> <li>• Changes from baseline in all domains of independent questions regarding the value of transfusion independence</li> <li>• Unscheduled (not scheduled per protocol) hospitalizations, office visits including consultations, laboratory and diagnostic tests (lab results, imaging etc.), and procedures prior to therapy initiation and during therapy will be collected</li> <li>• Composite of pharmacokinetic (PK) parameters of Eltrombopag including evaluation of covariates, and estimates of between and within subject variability</li> <li>• Composite of PK parameters of azacitidine (subset of 55 participants) including Cmax, tmax, AUC(0-t), AUC(0-infinity), and t1/2</li> <li>• Number of platelet transfusion-free cycles</li> </ul>
Starting date	June 2014
Contact information	<b>Sponsor:</b> US GSK Clinical Trials Call Center (Phone: 877-379-3718; Email: gskclinicalsupporthd@gsk.com)
Notes	<b>Expected number of participants:</b> 350 <b>Expected completion date:</b> December 2017

CMV: cytomegalovirus

ECOG: Eastern Cooperative Oncology Group

IPSS: International Prognostic Scoring System

MDS: myelodysplastic syndrome

PCR: polymerase chain reaction

## DATA AND ANALYSES

### Comparison 1. Thrombopoietin mimetic versus placebo

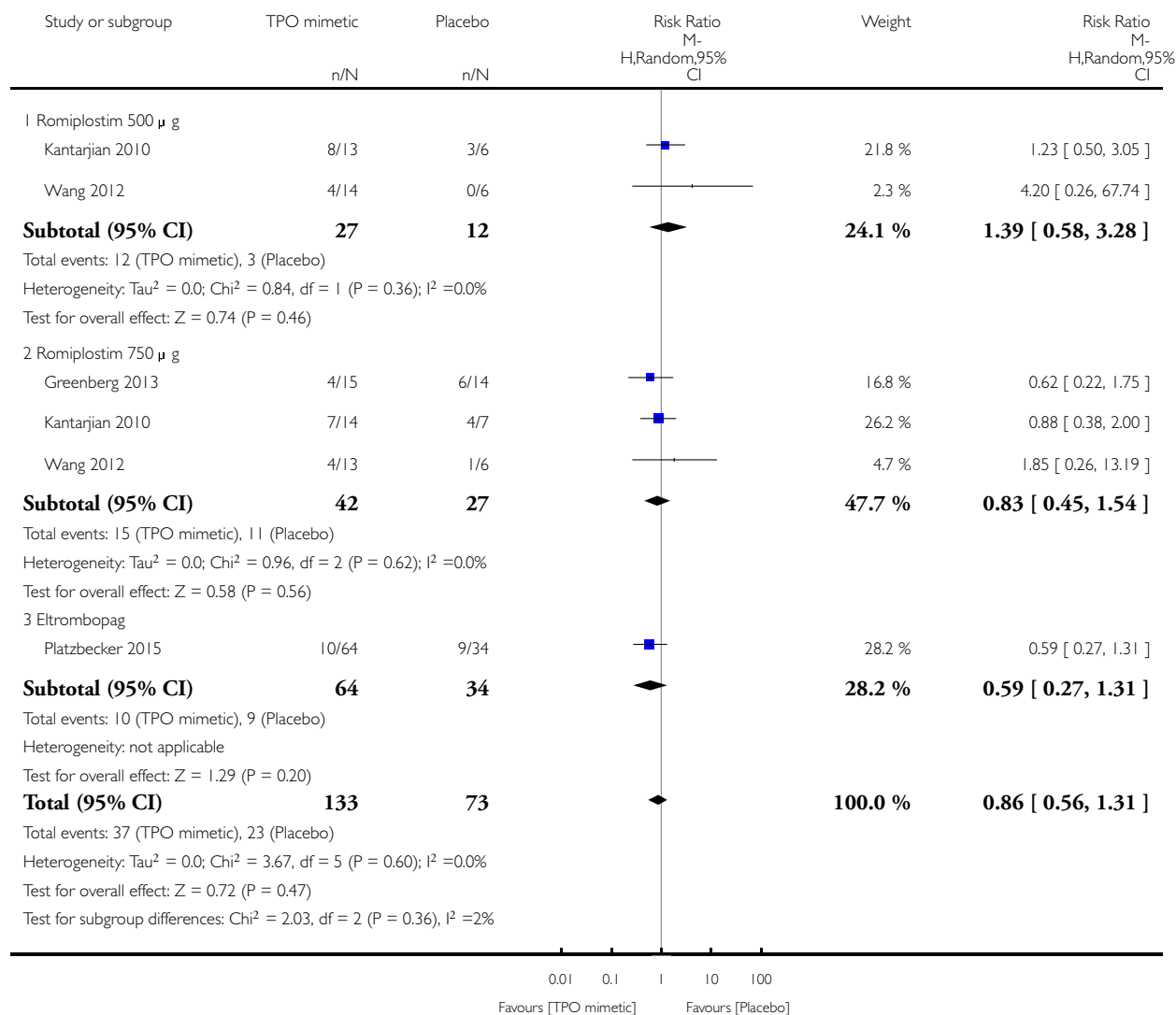
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least one bleeding episode	4	206	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.56, 1.31]
1.1 Romiplostim 500 µg	2	39	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.58, 3.28]
1.2 Romiplostim 750 µg	3	69	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.45, 1.54]
1.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.31]
2 Number of participants with at least one severe or life-threatening bleeding episode	1	40	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.04, 2.26]
2.1 Romiplostim 500 µg	1	19	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.03, 6.20]
2.2 Romiplostim 750 µg	1	21	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.88]
3 All-cause mortality	5	456	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.52, 1.05]
3.1 Romiplostim 500 µg	2	40	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 4.15]
3.2 Romiplostim 750 µg	4	318	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.49, 1.35]
3.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.42, 1.15]
4 Mortality due to bleeding	5	457	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.07, 2.69]
4.1 Romiplostim 500 µg	2	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Romiplostim 750 µg	4	319	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.22]
4.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.27, 6.49]
5 Mortality due to infection	4	206	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.32, 1.19]
5.1 Romiplostim 500 µg	2	40	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 4.15]
5.2 Romiplostim 750 µg	3	68	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.06, 3.24]
5.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.34, 1.41]
6 Proportion of participants receiving a platelet transfusion	4	206	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.61, 0.95]
6.1 Romiplostim 500 µg	2	39	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.44]
6.2 Romiplostim 750 µg	3	69	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.42, 1.15]
6.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.61, 1.02]
7 Transfusion reactions	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 Eltrombopag	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Thromboembolism	5	456	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.39, 5.01]
8.1 Romiplostim 500 µg	2	40	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Romiplostim 750 µg	4	318	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.23, 8.77]
8.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.10, 11.30]
9 Drug reactions	5	455	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.83, 1.51]
9.1 Romiplostim 500 µg	2	40	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.23, 1.70]
9.2 Romiplostim 750 µg	4	317	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.80, 1.70]
9.3 Eltrombopag	1	98	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.24, 2.63]

## Analysis 1.1. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 1 Number of participants with at least one bleeding episode.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 1 Number of participants with at least one bleeding episode

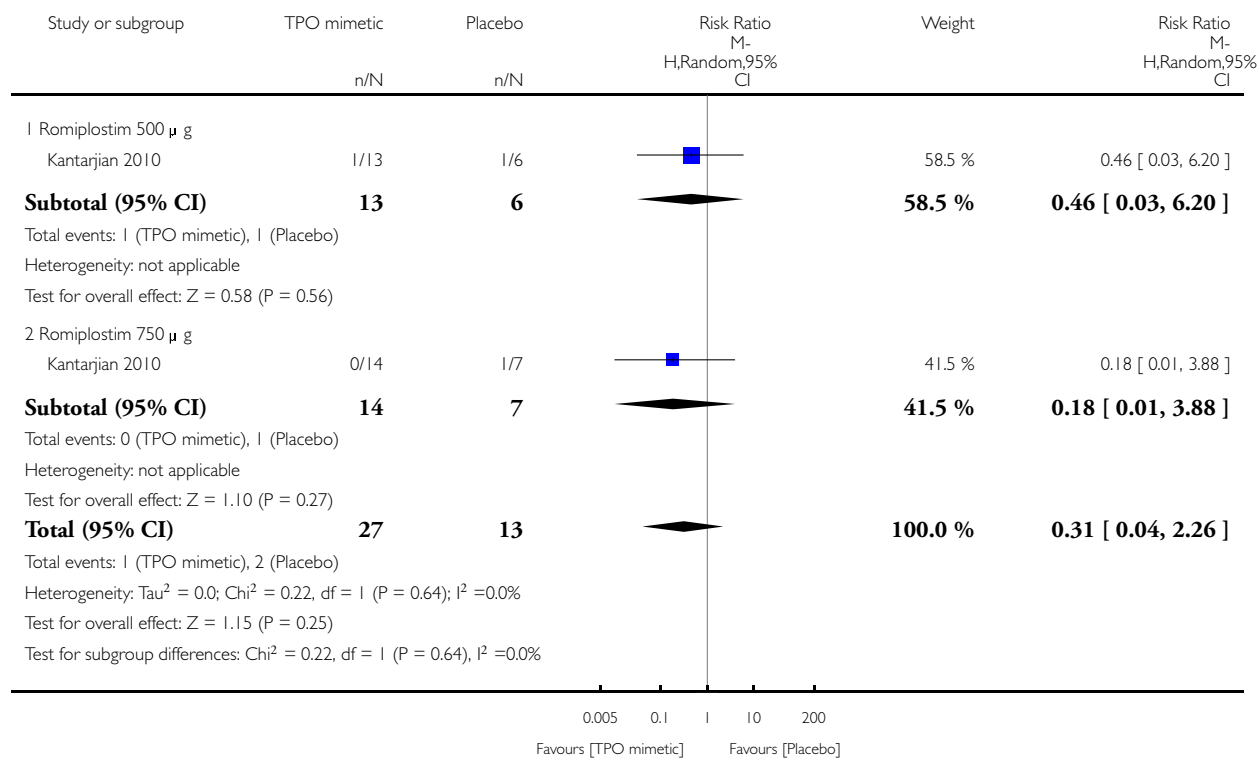


## Analysis 1.2. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 2 Number of participants with at least one severe or life-threatening bleeding episode.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 2 Number of participants with at least one severe or life-threatening bleeding episode

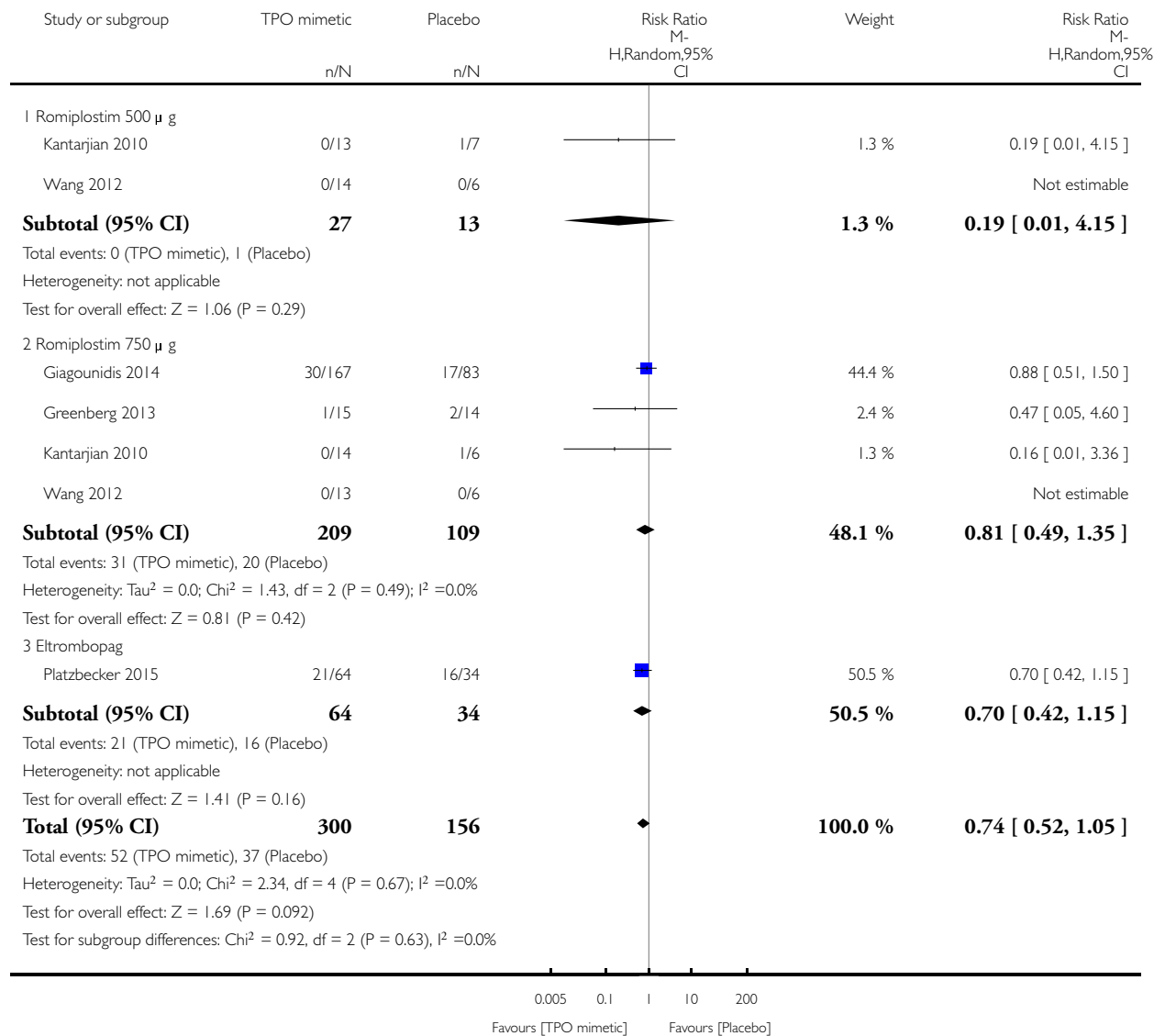


### Analysis 1.3. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 3 All-cause mortality.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 3 All-cause mortality

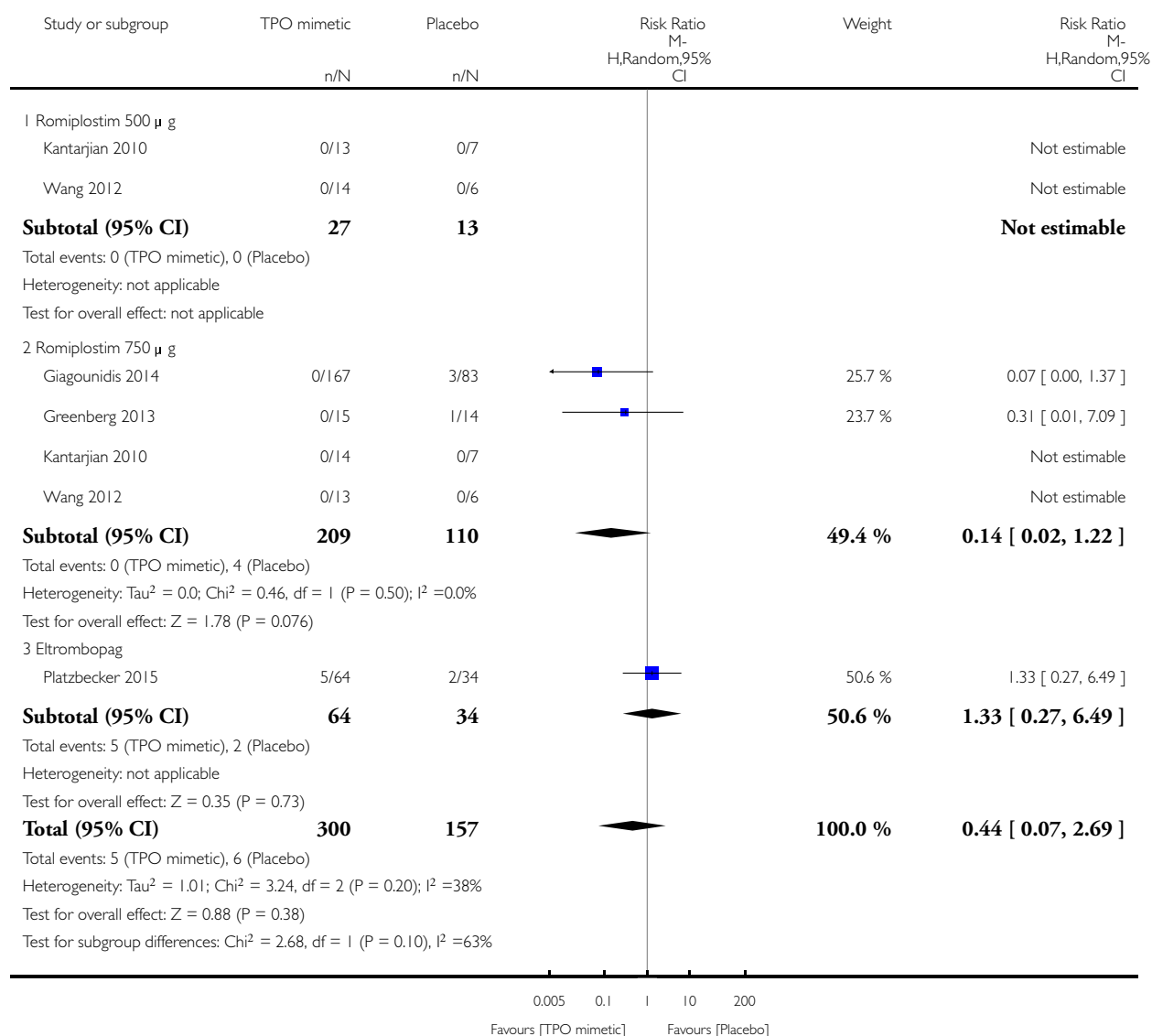


#### Analysis 1.4. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 4 Mortality due to bleeding.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 4 Mortality due to bleeding

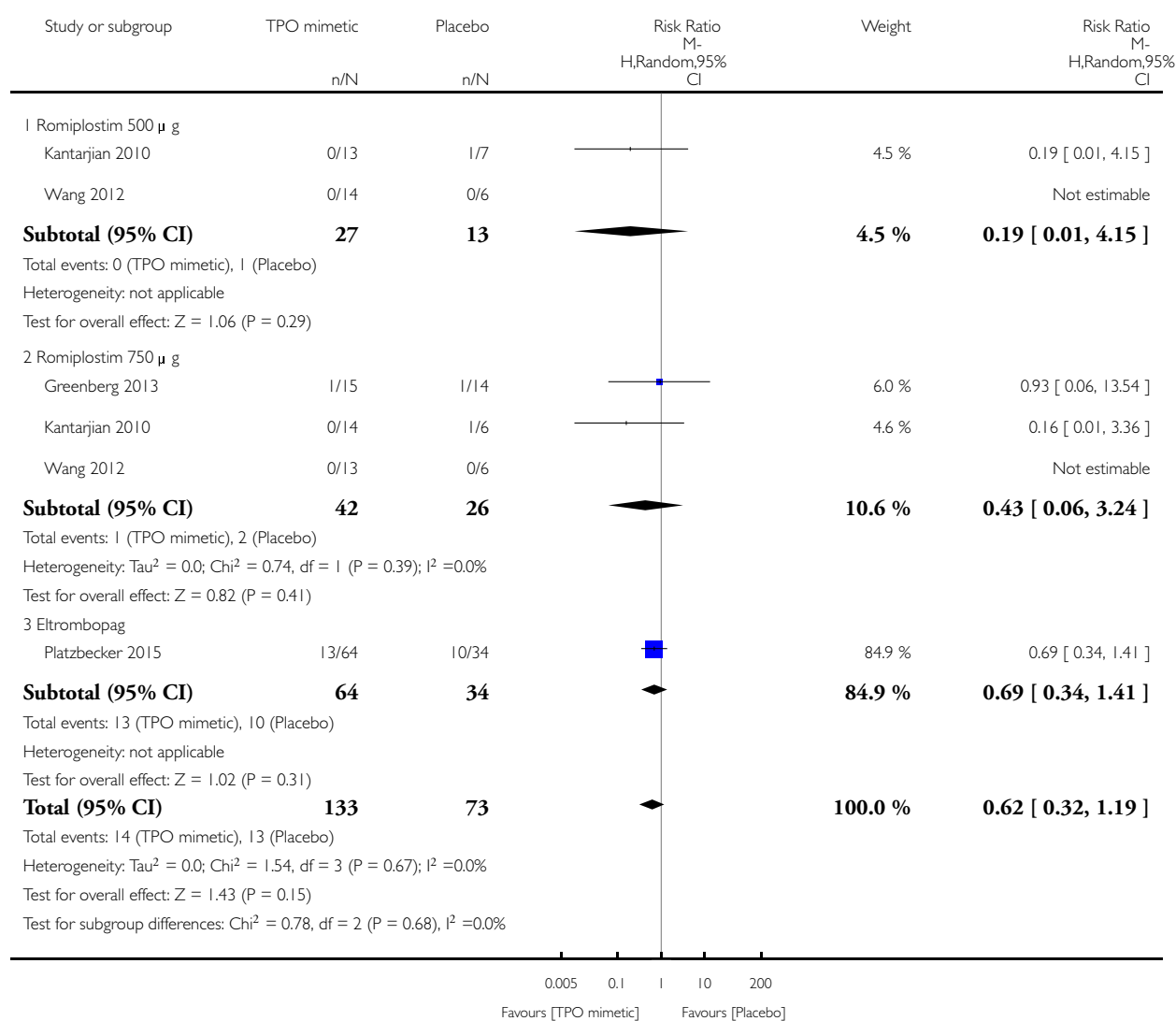


## Analysis 1.5. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 5 Mortality due to infection.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 5 Mortality due to infection



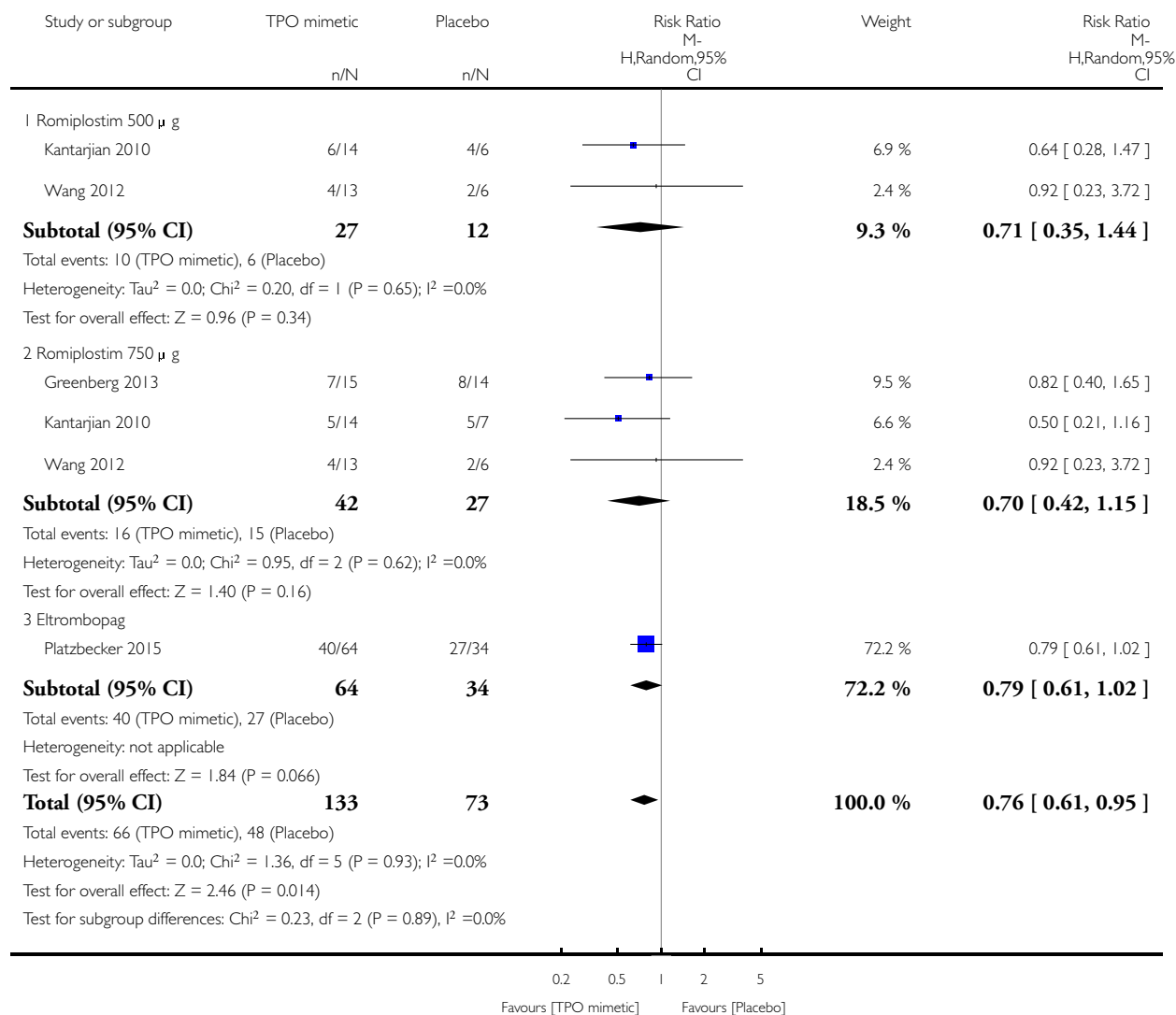


## Analysis 1.6. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 6 Proportion of participants receiving a platelet transfusion.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 6 Proportion of participants receiving a platelet transfusion

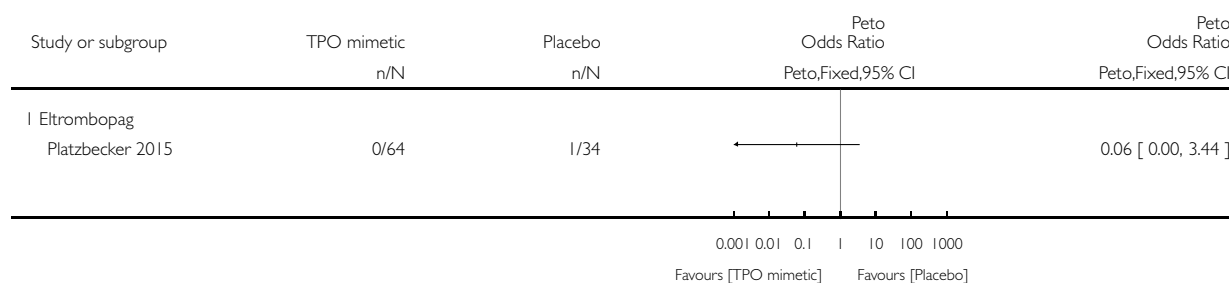


### Analysis I.7. Comparison I Thrombopoietin mimetic versus placebo, Outcome 7 Transfusion reactions.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: I Thrombopoietin mimetic versus placebo

Outcome: 7 Transfusion reactions

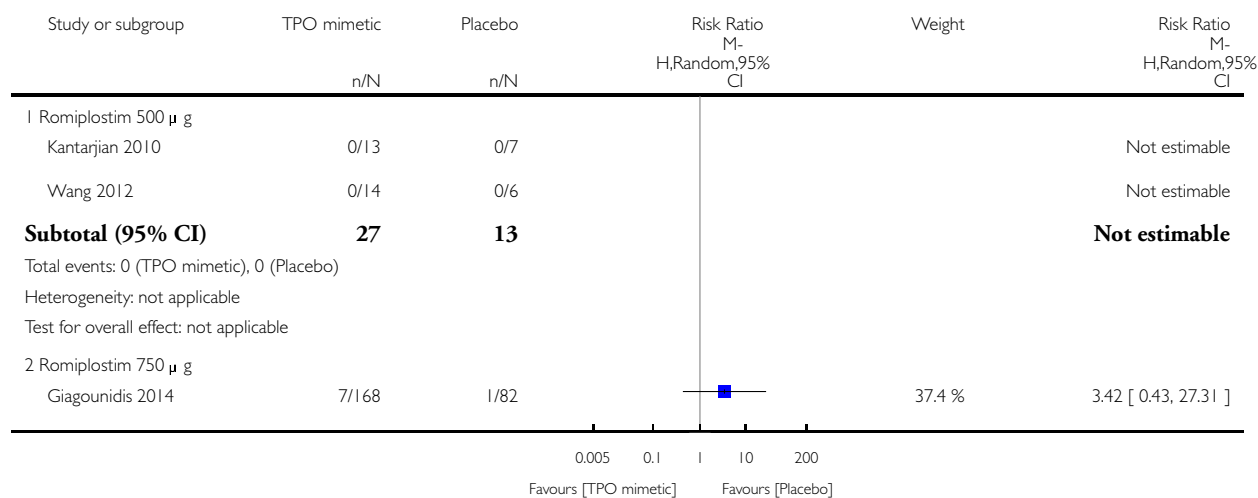


### Analysis I.8. Comparison I Thrombopoietin mimetic versus placebo, Outcome 8 Thromboembolism.

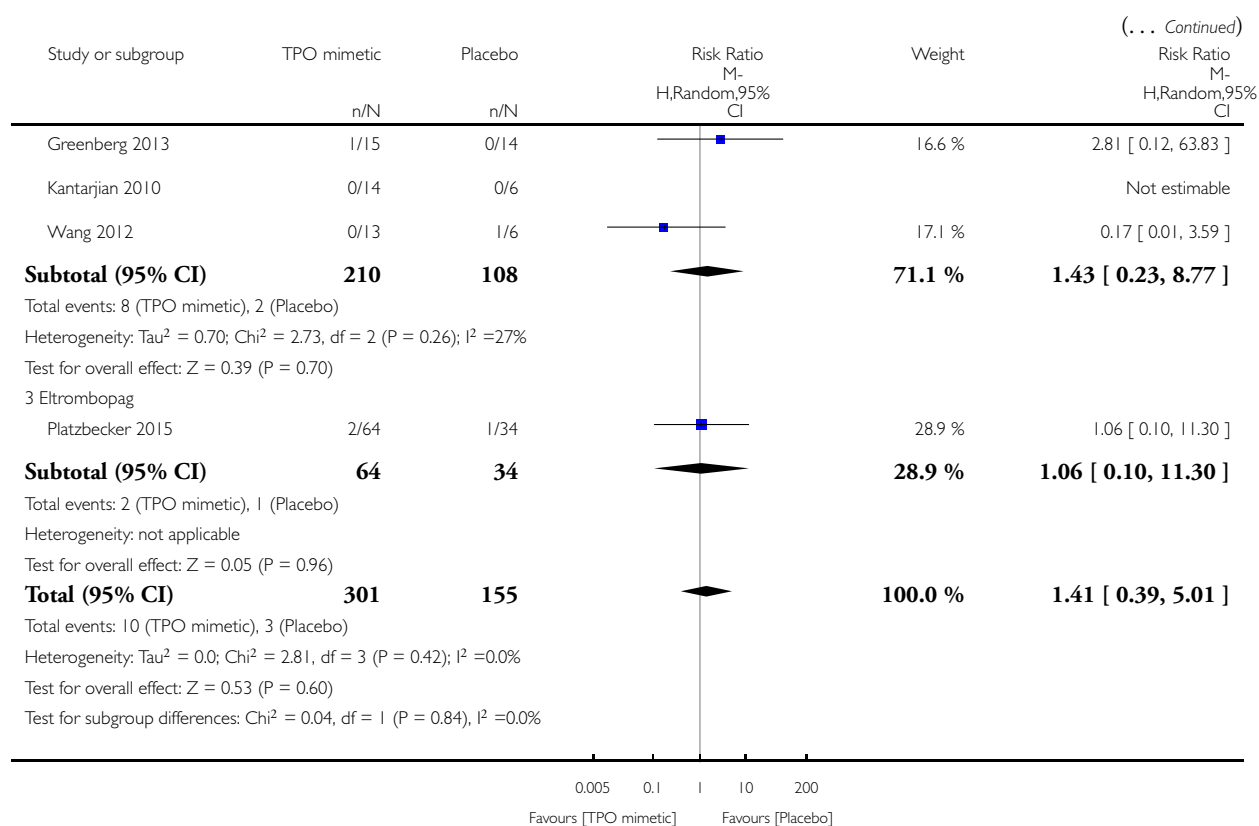
Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: I Thrombopoietin mimetic versus placebo

Outcome: 8 Thromboembolism



(Continued ...)

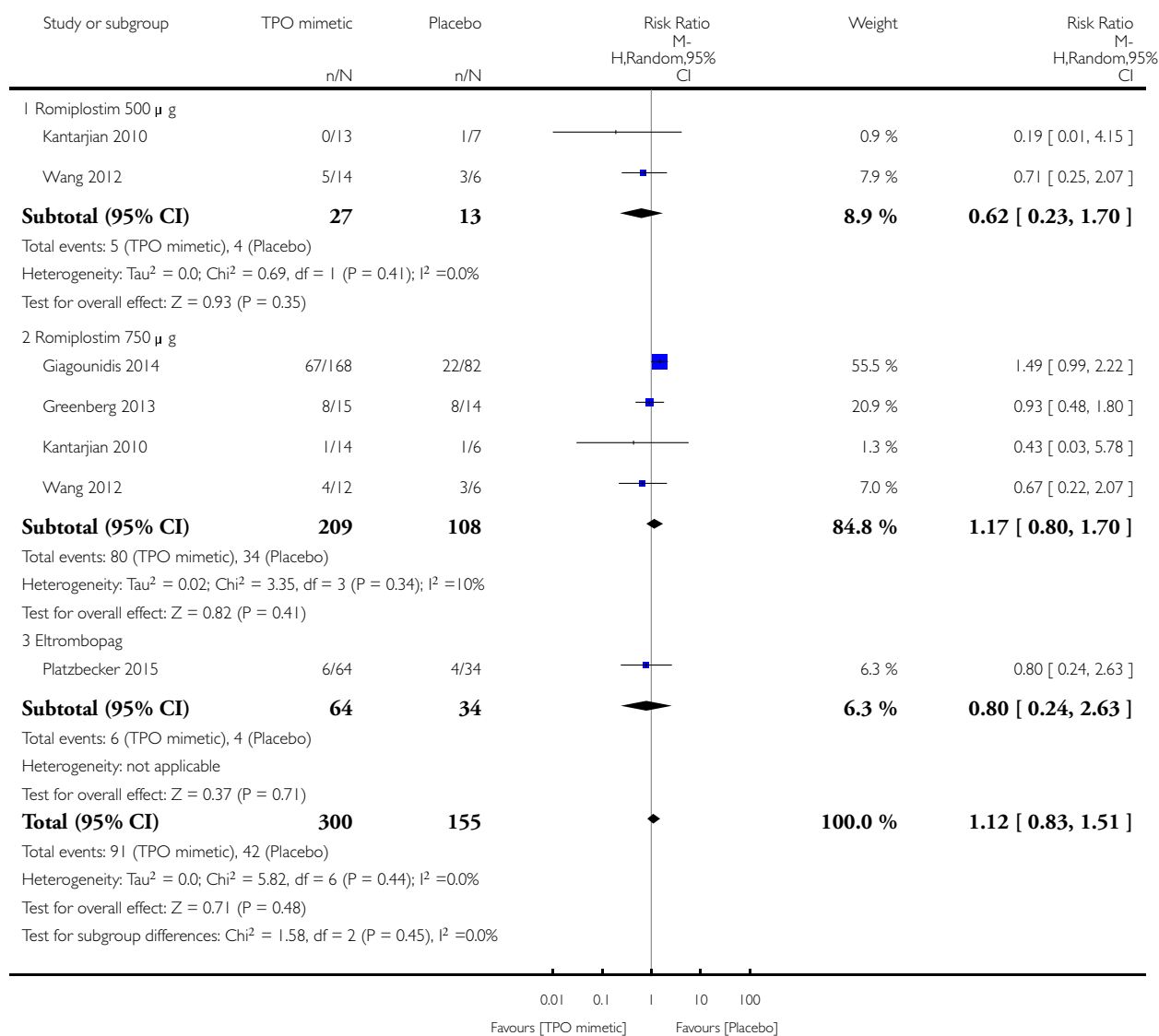


## Analysis 1.9. Comparison 1 Thrombopoietin mimetic versus placebo, Outcome 9 Drug reactions.

Review: Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review

Comparison: 1 Thrombopoietin mimetic versus placebo

Outcome: 9 Drug reactions



## ADDITIONAL TABLES

Table 1. Platelet transfusions per participant

Trial	Inclusion criteria (platelet count)	Duration of follow-up	Platelet transfusions per participant (mean)			
			Placebo	Romiplostim 500 µg	Romiplostim 750 µg	Eltrombopag
<a href="#">Kantarjian 2010</a>	Any	16 weeks	6.08	8.08	2.43	-
<a href="#">Wang 2012</a>	Any	16 weeks	3.92	0.21	6.23	-
<a href="#">Giagounidis 2014</a>	< 20 x 10 <sup>9</sup> /L or ≥ 20 and bleeding	26 weeks	15.6	-	11.1	-
<a href="#">Greenberg 2013</a>	Any	16-20 weeks	5.8	-	3.1	-
<a href="#">Platzbecker 2015</a>	< 30 x 10 <sup>9</sup> /L or transfusion dependent	26 weeks	28.8	-	-	37.8

Results reported as mean platelet transfusions per participant. Standard deviations not reported in any trial.

## APPENDICES

### Appendix I. CENTRAL search strategy

CENTRAL, DARE, HTA & NHSEED (the Cochrane Library 2016, Issue 3)

#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 aleukemic)) 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)

**Alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure: a meta-analysis and systematic review (Review)**

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#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 pancytopen\*

#14 (IMF or PMF or MDS):ti

#15 (bone marrow near/3 (fail\* or disease\* or disorder\* or aplasia or dysplasia or hypoplasia))

#16 (thrombocytopeni\* or leukemi\* or myelodysplas\* or myeloproliferat\* or shwachman diamond or (dyskeratosis next congenita\*) or AML)

#17 (fanconi\* next (anemia 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: [Factor VIIa] explode all trees

#20 (factor viia or factor 7a or rfviia or fvii or novoseven\* or novo seven\* or eptacog\* or proconvertin)

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

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

#23 #19 or #20 or #21 or #22

#24 MeSH descriptor: [Fibrinogen] explode all trees

#25 ("fibrinogen concentrate\*" or "factor I" or haemocomplettan\* or riastap\*)

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

#27 platelet-poor plasma\*

#28 #24 or #25 or #26 or #27

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

#30 (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)

#31 MeSH descriptor: [Thrombopoietin] explode all trees and with qualifier(s): [Administration & dosage - AD, Adverse effects - AE, Therapeutic use - TU]

#32 MeSH descriptor: [Recombinant Fusion Proteins] explode all trees and with qualifier(s): [Administration & dosage - AD, Adverse effects - AE, Therapeutic use - TU]

#33 MeSH descriptor: [Receptors, Fc] explode all trees and with qualifier(s): [Administration & dosage - AD, Therapeutic use - TU]

#34 MeSH descriptor: [Receptors, Thrombopoietin] explode all trees and with qualifier(s): [Administration & dosage - AD, Agonists - AG, Therapeutic use - TU]

#35 (eltrombopag\* or promacta\* or revolade\* or romiplastin\* or romiplostim\* or nplate)

#36 (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\*)

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

#38 #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37

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

#40 MeSH descriptor: [Interleukin-6] explode all trees

#41 MeSH descriptor: [Interleukin-11] this term only

#42 ("interleukin 6" or "interleukin 11" or IL6 or IL-6 or IL11 or IL-11 or sigosix or neumega or oprelvekin or rhIL-11 or INTLK11)

#43 #40 or #41 or #42

#44 MeSH descriptor: [Factor XIII] explode all trees

#45 factor xiii\* or fxiii\* or rfxiii\* or stabilizing factor fibrin or fibrin stabilizing factor or laki-lorand factor or fibrinase or corifact or fibrogammin or tretten

#46 #44 or #45

#47 #23 or #28 or #38 or #39 or #43 or #46

#48 #18 and #47

#49 MeSH descriptor: [Antifibrinolytic Agents] this term only

#50 MeSH descriptor: [Tranexamic Acid] this term only

#51 MeSH descriptor: [Aminocaproic Acid] this term only

#52 MeSH descriptor: [Aprotinin] this term only

#53 antifibrinolytic\* or anti-fibrinolytic\* or antiplasmin\* or "plasmin inhibitor\*" or tranexamic or tranhexamic or "cyclohexanecarboxylic acid" or amcha or "trans-4-aminomethyl-cyclohexanecarboxylic acid" or "t-amcha" or amca or "kabi 2161" or transamin or exacyl or amchafibrin or anvitoff or spotof or cyklokapon or ugurol or amstat or antivoff or caprilon or aminomethylcyclohexanecarbonic

or aminomethylcyclohexanecarboxylic or AMCHA or amchafibrin or amikapron or “aminomethyl cyclohexane carboxylic acid” or “aminomethyl cyclohexanecarboxylic acid” or “aminomethylcyclohexane carbonic acid” or “aminomethylcyclohexane carboxylic acid” or “aminomethylcyclohexanecarbonic acid” or “aminomethylcyclohexanecarboxylic acid” or “aminomethylcyclohexanocarboxylic acid” or “aminomethylcyclohexanoic acid” or “cl 65336” or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or “trans achma” or transexamic or trenaxin or TXA

#54 Agretax or Bio-Stat or Capiloc or Capitrax or “Clip Inj” or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or “Sylstep TX” or Synostat or T-nex or T-Stat or Tanmic or Temsyt-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or “Trance Inj” or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or “Trim Inj” or Tx-1000 or Tx-500 or Wistran or X-Tran or Xamic

#55 aminocaproic or aminohexanoic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin\* or caprolysin\* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or “cl 10304” or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or “epsilon amino caproate” or “epsilon aminocaproate” or epsilonaminocaproic or epsilonaminocapronsav or ethaaminocaproic or ethaaminocaproic or emocaprol or hepin or ipsilon or jd177 or neocaprol or nsc26154 or resplamin or tachostyptan

#56 aprotinin\* or antagosan or antilysin\* or apronitin\* or apronitrine or aprotimbin or aprotonin\* or “bayer a 128” or “bayer a128” or contrical or contrycal or contrykal or dilmintal or “frey inhibitor” or gordox or haemoprot or iniprol or kontrikal or kontrycal or “Kunitz inhibitor” or “Kunitz trypsin inhibitor” or midran or “pancreas antitrypsin” or “pancreatic antitrypsin” or protinin or pulmin or “riker 52g” or rivilina or “rp 9921” or rp9921 or tracylol or trascolan or trasilol or traskolan or trasylol or trazylol or “trypsin inhibitor” or zymofren or zymophren

#57 #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56

#58 #18 and #57

#59 #48 or #58

## Appendix 2. MEDLINE search strategy

MEDLINE (1946 to 27 April 2016)

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,ot.
9. (thrombocytopeni\* or thrombop?en\* or leuk?emi\* or myeloproliferat\* or shwachman diamond or (dyskeratosis adj1 congenita\*) or AML).tw,kf,ot.
10. (myelodysplas\* or myeloid dysplasia or preleukemi\* or preleukaemi\* or dysmyelopoie\* or 5Q syndrome).tw,kf,ot.
11. ((aplast\* or hypoplast\* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic\*) adj2 an?emia).tw,kf,ot.
12. (erythroid aplasia or erythrodysplas\* or hematopoietic aplasia or pancytopen\*).tw,kf,ot.
13. (fanconi\* adj (an?emia or panmyelopathy or syndrome)).tw,kf,ot.
14. ((myelos\* adj2 nonleukemic) or (myeloid adj2 metaplasia\*) or myelofibros\* or (bone marrow adj5 fibros\*) or myeloscleros\*).tw,kf,ot.
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,ot.
17. ((haematolog\* or hematolog\* or haemato-oncolog\* or hemato-oncolog\*) adj2 patients).tw,kf,ot.
18. or/1-17
19. Factor VIIa/
20. (factor viia or factor 7a or rfviia or fviia or novoseven\* or novo seven\* or eptacog\* or proconvertin).tw.

21. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvi) or (activated adj2 fvii)).tw.
22. (factor seven or factor vii or factor 7).ti.
23. or/19-22
24. Fibrinogen/ad, ae, sd, tu, th
25. \*Fibrinogen/
26. (fibrinogen concentrate\* or factor I or haemocomplettan\* or riastap\*).tw.
27. or/24-26
28. ((platelet\* or thrombocyte\*) adj5 (substitute\* or artificial\*)).tw.
29. platelet-poor plasma\*.tw.
30. \*Deamino Arginine Vasopressin/
31. Deamino Arginine Vasopressin/ad, ae, st, tu, to
32. (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 adiuretin or octostim or desmogalen).tw.
33. or/28-32
34. Thrombopoietin/ad, tu
35. Recombinant Fusion Proteins/ad, tu
36. Receptors, Fc/ad, tu
37. Receptors, Thrombopoietin/ad, ag, ai, tu
38. (eltrombopag\* or promacta\* or revolade\* or SB-497115-GR or romiplostim\* or nplate\* or AMG-31 or AMG31).tw.
39. (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.
40. ((TPO or thrombopoietin) adj (mimetic\* or receptor agonist\* or agonist\* or agent\*)).tw.
41. or/34-40
42. (((haemosta\* or hemosta\* or antihemorrhag\* or antihemorrhag\* or anti haemorrhag\* or anti-hemorrhag\*) adj5 (drug\* or agent\* or treat\* or therap\*)) or ((coagulat\* or clotting) adj factor\*)).tw.
43. Interleukin-6/
44. ("interleukin 6" or IL6 or IL-6 or sigosix).tw.
45. Interleukin-11/
46. ("interleukin 11" or IL11 or IL-11 or neumega or oprelvekin or rhIL-11 or Intlk11).tw.
47. or/43-46
48. exp Factor XIII/
49. (factor xiii\* or fxiii\* or rfxiii\* or stabili?ing factor fibrin or fibrin stabili?ing factor or laki lorand factor or fibrinase or corifact or fibrogammin or tretten).tw.
50. or/48-49
51. 23 or 27 or 33 or 41 or 42 or 47 or 50
52. randomized controlled trial.pt.
53. controlled clinical trial.pt.
54. randomi\*.tw.
55. placebo.ab.
56. clinical trials as topic.sh.
57. randomly.ab.
58. groups.ab.
59. trial.ti.
60. or/52-59
61. Animals/ not Humans/
62. 60 not 61
63. Antifibrinolytic Agents/
64. Tranexamic Acid/
65. Aminocaproic Acid/
66. Aprotinin/
67. (antifibrinolytic\* or anti-fibrinolytic\* or antiplasmin\* or plasmin inhibitor\* or tranexamic or tranhexamic or cyclohexanecarboxylic acid\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or "kabi 2161" or transamin or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecar-



boxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA).tw.

68. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyt-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw.

69. (amino?caproic or amino?hexanoic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin\* or caprolysin\* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177 or neocaprol or nsc? 26154 or resplamin or tachostyptan).tw.

70. (aprotinin or antagosan or antilysin\* or apronitin\* or apronitrine or aprotimbin or aprotinine or aprotonin or "bayer a 128" or "bayer a128" or bovine pancreatic secretory trypsin inhibitor or contrical or contrycal or contrykal or dilmintal or frey inhibitor or gordox or haemoprot or iniprol or kallikrein trypsin inhibitor or kazal type trypsin inhibitor or kontrikal or kontrycal or Kunitz inhibitor or Kunitz trypsin inhibitor or midran or pancreas antitrypsin or pancreas secretory trypsin inhibitor or pancreas trypsin inhibitor or pancreatic antitrypsin or pancreatic secretory trypsin inhibitor or pancreatic trypsin inhibitor or protinin or pulmin or "riker 52g" or rivilina or "rp 9921" or rp9921 or tracylol or trascolan or trasilol or traskolan or trasylol or trazyol or trypsin inhibitor or zymofren or zymophren).tw.

71. or/63-70

72. 51 or 71

73. 18 and 72 and 62

### Appendix 3. Embase search strategy

Embase (1974 to 27 April 2016)

1. Hematologic Malignancy/
2. exp Myeloproliferative Disorder/
3. exp Aplastic Anemia/
4. exp Thrombocytopenia/
5. (bone marrow adj3 (fail\* or disease\* or disorder\* or aplasia or hypoplasia or dysplasia)).tw,kf,ot.
6. ((myelos\* adj2 nonleukemic) or (myeloid adj2 metaplasia\*) or myelofibros\* or (bone marrow adj5 fibros\*) or myeloscleros\*).tw,kf,ot.
7. (thrombocytopeni\* or thrombop?en\* oro leuk?emi\* or myeloproliferat\* or shwachman diamond or (dyskeratosis adj1 congenita\*) or AML).tw,kf,ot.
8. (erythroid aplasia or erythrodysplas\* or hematopoietic aplasia or pancytopen\*).tw,kf,ot.
9. (fanconi\* adj (an?emia or panmyelopathy or syndrome)).tw.
10. ((haematolog\* or hematolog\* or haemato-oncolog\* or hemato-oncolog\*) adj2 patients).tw,kf,ot.
11. ((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,ot.
12. exp Myelodysplastic Syndrome/
13. Myelodysplasia/ or Preleukemia/
14. (myelodysplas\* or myeloid dysplasia or preleukemi\* or preleukaemi\* or dysmyelopoie\* or 5Q syndrome).tw,kf,ot.
15. ((aplast\* or hypoplast\* or refractory or aregenerative or sideroblastic or sideroachrestic or chronic\*) adj2 an?emia).tw,kf,ot.
16. (MDS or IMF or PMF).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. or/18-21
23. Fibrinogen/ae, ct, ad, cb, cm, cr, dv, do, dt, to, iv, pa, sc, th
24. Fibrinogen Concentrate/
25. (fibrinogen concentrate\* or factor I or haemocomplettan\* or riastap\*).tw.
26. or/23-25
27. ((platelet\* or thrombocyte\*) adj5 (substitute\* or artificial\*)).tw.
28. platelet-poor plasma\*.tw.
29. \*Desmopressin/
30. Desmopressin/ad, ae, dt
31. (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.
32. or/27-31
33. \*Thrombopoietin Receptor/
34. Eltrombopag/
35. Romiplostim/
36. (eltrombopag\* or promacta\* or revolade\* or SB-497115-GR or romiplostim\* or nplate\* or AMG-31 or AMG31).tw.
37. (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.
38. ((TPO or thrombopoietin) adj (mimetic\* or receptor agonist\* or agonist\*)).tw.
39. or/33-38
40. (((haemosta\* or hemosta\* or antihemorrhag\* or antihemorrhag\* or anti haemorrhag\* or anti-hemorrhag\*) adj5 (drug\* or agent\* or treat\* or therap\*)) or ((coagulat\* or clotting) adj factor\*)).tw.
41. blood clotting factor 13/ or blood clotting factor 13 concentrate/ or blood clotting factor 13a/ or blood clotting factor 13b/
42. (factor xiii\* or fxiii or rfxiii or stabili?ing factor fibrin or fibrin stabili?ing factor or laki lorand factor or fibrinase or corifact or fibrogammin or tretten).tw.
43. or/41-42
44. \*interleukin 6/
45. interleukin 6/ae, ct, ad, an, cb, cm, cr, dv, do, it, dt, to, ei, ih, ar, ce, cv, ci, dl, ig, ly, im, na, ip, pl, sp, tl, tr, tu, iv, vi, po, pr, pe, pk, pd, rc, cj, sc, tp
46. ("interleukin 6" or IL6 or IL-6).ti.
47. interleukin 11/
48. ("interleukin 11" or IL11 or IL-11 or sigosix or neumega or oprelvekin or rhIL-11 or INTLK11).tw.
49. or/44-48
50. 22 or 26 or 32 or 39 or 40 or 43 or 49
51. Randomized Controlled Trial/
52. Randomization/
53. Single Blind Procedure/
54. Double Blind Procedure/
55. Crossover Procedure/
56. Placebo/
57. exp Clinical Trial/
58. Prospective Study/
59. (randomi\* or double-blind\* or single-blind\* or RCT\*).tw.
60. (random\* adj2 (allocat\* or assign\* or divid\* or receiv\*)).tw.
61. (crossover\* or cross over\* or cross-over\* or placebo\*).tw.
62. ((treble or triple) adj blind\*).tw.
63. or/51-62
64. Case Study/
65. case report\*.tw.
66. (note or editorial).pt.

67. or/64-66  
 68. 63 not 67  
 69. exp Antifibrinolytic Agents/  
 70. (antifibrinolytic\* or anti-fibrinolytic\* or antiplasmin\* or plasmin inhibitor\* or tranexamic or tranhexamic or cyclohexanecarboxylic acid\* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid\* or t-amcha or amca or “kabi 2161” or transamin or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklokapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA).tw.  
 71. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Tranxi or Trapic or Traxage or Traxamic or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw.  
 72. (amino?caproic or amino?hexanoic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin\* or caprolysin\* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc? 26154 or resplamin or tachostyptan).tw.  
 73. (aprotinin or antagosan or antilysin\* or apronitin\* or apronitrine or aprotimbin or aprotinine or aprotonin or “bayer a 128” or “bayer a128” or bovine pancreatic secretory trypsin inhibitor or contrical or contrycal or contrykal or dilmintal or frey inhibitor or gordox or haemoprot or iniprol or kallikrein trypsin inhibitor or kazal type trypsin inhibitor or kontrikal or kontrycal or Kunitz inhibitor or Kunitz trypsin inhibitor or midran or pancreas antitrypsin or pancreas secretory trypsin inhibitor or pancreas trypsin inhibitor or pancreatic antitrypsin or pancreatic secretory trypsin inhibitor or pancreatic trypsin inhibitor or protinin or pulmin or “riker 52g” or rivilina or “rp 9921” or rp9921 or tracylol or trascolan or trasilol or traskolan or trasylol or trazylol or trypsin inhibitor or zymofren or zymophren).tw.  
 74. or/69-73  
 75. 50 or 74  
 76. 17 and 75 and 68  
 77. limit 76 to embase

#### Appendix 4. CINAHL search strategy

CINAHL (1937 to 27 April 2016)  
 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 aleukemic)) or (myeloid N2 metaplasia\*) or myelofibros\* or (bone marrow N5 fibros\*) or myelosclerosis\*)  
 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 Coagulation Factors+")  
 S17 (factor viia or factor 7a or rfviia or fviiia or novoseven\* or novo seven\* or eptacog\* or proconvertin\* or fibrinogen concentrate\* or factor I or haemocomplettan\* or riastap\*)  
 S18 ((activated N2 factor seven) or (activated N2 factor vii) or (activated N3 rfvii) or (activated N2 fvii))  
 S19 TI (factor seven or factor vii or factor 7)  
 S20 S16 OR S17 OR S18 OR S19  
 S21 ((platelet\* or thrombocyte\*) N5 (substitute\* or artificial\*))  
 S22 platelet-poor plasma\*  
 S23 (MH "Desmopressin")  
 S24 (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)  
 S25 S21 OR S22 OR S23 OR S24  
 S26 (MH "Benzoic Acids Therapeutic Use")  
 S27 (MH "Receptors, Cell Surface Therapeutic Use")  
 S28 (eltrombopag\* or promacta\* or revolade\* or romiplostin\* or romiplostim\* or nplate or TPO\*)  
 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 S26 OR S27 OR S28 OR S29 OR S30  
 S32 (((haemosta\* or hemosta\* or antihemorrhag\* or antihemorrhag\* or anti haemorrhag\* or anti-hemorrhag\*) N5 (drug\* or agent\* or treat\* or therap\*)) or ((coagulat\* or clotting) W1 factor\*))  
 S33 S20 OR S25 OR S31 OR S32  
 S34 S15 AND S33  
 S35 (MH Clinical Trials+)  
 S36 PT Clinical Trial  
 S37 TI ((controlled trial\*) or (clinical trial\*)) OR AB ((controlled trial\*) or (clinical trial\*))  
 S38 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\*))  
 S39 TI randomi\* OR AB randomi\*  
 S40 MH RANDOM ASSIGNMENT  
 S41 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))  
 S42 ( TI (random\* N2 (assign\* or allocat\*)) ) OR ( AB (random\* N2 (assign\* or allocat\*)) )  
 S43 MH PLACEBOS  
 S44 MH META ANALYSIS  
 S45 MH SYSTEMATIC REVIEW  
 S46 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\*")  
 S47 TI ("literature review" OR "literature overview" OR "literature search\*") OR AB ("literature review" OR "literature overview" OR "literature search\*")  
 S48 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)  
 S49 TI placebo\* OR AB placebo\*  
 S50 MH QUANTITATIVE STUDIES  
 S51 S35 or S36 or 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  
 S52 S34 AND S51  
 S53 (MM "Interleukins")  
 S54 "interleukin 6" or "interleukin 11" or IL6 or IL-6 or IL11 or IL-11 or sigosix or neumega or oprelvekin or rhIL-11 or INTLK11

S55 factor xiii\* or fxiii\* or rfxiii\* or stabilizing factor fibrin or fibrin stabilizing factor or laki-lorand factor or fibrinase or corifact or fibrogammin or tretien  
 S56 S53 OR S54 OR S55  
 S57 S33 OR S56  
 S58 S15 AND S51 AND S57  
 S59 (MH "Antifibrinolytic Agents")  
 S60 (MH "Aminocaproic Acids")  
 S61 (MH "Tranexamic Acid")  
 S62 (MH "Aprotinin")  
 S63 TI ( (antifibrinolytic\* or anti-fibrinolytic\* or antiplasmin\* or "plasmin inhibitor\*" or tranexamic or tranhexamic or "cyclohexanecarboxylic acid" or amcha or "trans-4-aminomethyl-cyclohexanecarboxylic acid" or "t-amcha" or amca or "kabi 2161" or transamin or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol or amstat or antivoff or caprilon or aminomethylcyclohexanecarboxylic or aminomethylcyclohexanecarboxylic or AMCHA or amchafibrin or amikapron or "aminomethyl cyclohexane ca ...  
 S64 TI ( (Agretax or Bio-Stat or Capiloc or Capitrax or "Clip Inj" or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nixa-500 or Rheonex or "Sylstep TX" or Synostat or T-nex or T-Stat or Tanmic or Temsyt-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or "Trance Inj" or Tranecid or Tranee or ...  
 S65 TI ( (aminocaproic or aminohexanoic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin\* or caprolysin\* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or "cl 10304" or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or "epsilon amino caproate" or "epsilon amino ...  
 S66 TI ( (aprotinin\* or antagosan or antilysin\* or apronitin\* or apronitrine or aprotimbin or aprotonin\* or "bayer a 128" or "bayer a128" or contrycal or contrycal or contrykal or dilmintal or "frey inhibitor" or gordox or haemoprot or iniprol or kontrikal or kontrycal or "Kunitz inhibitor" or "Kunitz trypsin inhibitor" or midran or "pancreas antitrypsin" or "pancreatic antitrypsin" or protinin or pulmin or "riker 52g" or rivilina or "rp 9921" or rp9921 or tracylol or trascolan or trasilol or trasko ...  
 S67 S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66  
 S68 S57 OR S67  
 S69 S15 AND S51 AND S68

## Appendix 5. PubMed epublications search strategy

PUBMED (epublications only)

#1 (bone marrow failure OR bone marrow disease\* or bone marrow disorder\* OR bone marrow aplasia OR bone marrow dysplasia OR bone marrow hypoplasia 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 a regenerative anemia OR aregenerative anaemia OR chronic anemia OR chronic anaemia OR fanconi OR erythroid aplasia OR erythrodysplas\* OR hematopoietic aplasia OR haematopoietic aplasia OR pancytopen\*)  
 #2 (thrombocytopenia\* OR leukemia\* OR leukaemia\* OR preleuk\* OR myelodysplas\* OR myeloproliferat\* OR myelofibros\* OR myelosclerosis\* OR shwachman diamond OR dyskeratosis congenital OR AML OR dysmyelopoie\* or 5Q syndrome)  
 #3 ((haematolog\* OR hematolog\* OR blood OR red cell\* OR white cell\* OR marrow OR platelet\*) AND (malignan\* OR oncolog\* OR cancer OR cancers OR neoplasm\* or carcinoma\*))  
 #4 ((myelos\* AND (nonleukemic OR aleukemic)) OR (myeloid AND metaplasia\*) OR (bone marrow AND fibros\*))  
 #5 IMF[TI] OR PMF[TI] OR MDS[TI]  
 #6 (haematolog\* patients OR hematolog\* patients OR haemato-oncolog\* patients OR hemato-oncolog\* patients)  
 #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6  
 #8 ("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])  
 #9 "activated factor seven"[TI] OR "activated factor vii"[TI] OR "activated rfvii"[TI] OR "activated fvii"[TI] OR "factor seven"[TI] OR "factor vii"[TI] OR "factor 7"[TI]  
 #10 ((platelet\* OR thrombocyte\*) AND (substitute\* OR artificial\*))  
 #11 ("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 adiuretin OR octostim OR desmogalen)

#12 (eltrombopag\* OR promacta\* OR revolade\* OR romiplastin\* OR romiplostim\* OR nplate\*)

#14 ("interleukin 6" OR "interleukin 11" OR IL6 OR IL-6 OR IL11 OR IL-11 OR sigosix OR neumega OR oprelvekin OR rhIL-11 OR INTLK11)

#15 (factor xiii\* OR fxiii\* OR rfxiii\* OR stabilizing factor fibrin OR stabilising factor fibrin OR fibrin stabilizing factor OR fibrin stabilising factor OR laki lorand factor OR fibrinase OR corifact OR fibrogammin OR tretien)

#16 (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\*)

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

#18 ((haemosta\* OR hemosta\* OR antihemorrhag\* 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))

#19 (antifibrinolytic[TI] OR anti-fibrinolytic[TI] OR antifibrinolytics[TI] OR anti-fibrinolytics[TI] OR antiplasmin[TI] OR antiplasmins[TI] OR "plasmin inhibitor\*" [TI] OR tranexamic[TI] OR tranhexamic[TI] OR "cyclohexanecarboxylic acid" [TI] OR amcha[TI] OR "trans-4-aminomethyl-cyclohexanecarboxylic acid" [TI] OR "t-amcha" [TI] OR amca[TI] OR "kabi 2161" [TI] OR transamin[TI] OR exacyl[TI] OR amchafibrin[TI] OR anvitoff[TI] OR spotof[TI] OR cyklokapron[TI] OR ugurol[TI] OR amstat[TI] OR antivoff[TI] OR caprilon[TI] OR aminomethylcyclohexanecarbonic[TI] OR aminomethylcyclohexanecarboxylic[TI] OR AMCHA[TI] OR amchafibrin[TI] OR amikapron[TI] OR "aminomethyl cyclohexane carboxylic acid" [TI] OR "aminomethyl cyclohexanecarboxylic acid" [TI] OR "aminomethylcyclohexane carbonic acid" [TI] OR "aminomethylcyclohexane carboxylic acid" [TI] OR "aminomethylcyclohexanecarbonic acid" [TI] OR "aminomethylcyclohexanecarboxylic acid" [TI] OR "aminomethylcyclohexanecarboxylic acid" [TI] OR "aminomethylcyclohexanoic acid" [TI] OR "cl 65336" [TI] OR cl65336[TI] OR cyclocapron[TI] OR cyclokapron[TI] OR cyklocapron[TI] OR cyklokapron[TI] OR exacyl[TI] OR frenolyse[TI] OR fibrinon[TI] OR hemostan[TI] OR hexacapron[TI] OR hexakapron[TI] OR kalnex[TI] OR lysteda[TI] OR rikaparin[TI] OR ronex[TI] OR theranex[TI] OR tranexam[TI] OR tranexanic[TI] OR tranexic[TI] OR "trans achma" [TI] OR tranexamic[TI] OR trenaxin[TI] OR TXA[TI] OR Agretax[TI] OR Bio-Stat[TI] OR Capiloc[TI] OR Capitrax[TI] OR "Clip Inj" [TI] OR Clot-XL[TI] OR Clotawin-T[TI] OR Coastat[TI] OR Cuti[TI] OR Cymin[TI] OR Dubatran[TI] OR Examic[TI] OR Existat[TI] OR Extam[TI] OR Fibran[TI] OR Gynae-Pil[TI] OR Hemstate[TI] OR Menogia[TI] OR Monitex[TI] OR Nestrin[TI] OR Nexamic[TI] OR Nexi-500[TI] OR Nexmeff[TI] OR Nixa-500[TI] OR Rheonex[TI] OR "Sylstep TX" [TI] OR Synostat[TI] OR T-nex[TI] OR T-Stat[TI] OR Tanmic[TI] OR Temsyl-T[TI] OR Texakind[TI] OR Texanis[TI] OR Texapar[TI] OR Texid[TI] OR Thams[TI] OR Tonopan[TI] OR Traklot[TI] OR Tramic[TI] OR Tramix[TI] OR Tranarest[TI] OR "Trance Inj" [TI] OR Tranecid[TI] OR Tranee[TI] OR Tranemic[TI] OR Tranex[TI] OR Tranexa[TI] OR Tranfib[TI] OR Tranlok[TI] OR Transtat[TI] OR Transys[TI] OR Tranxi[TI] OR Trapic[TI] OR Traxage[TI] OR Traxamic[TI] OR Trenaxa[TI] OR Trexamic[TI] OR "Trim Inj" [TI] OR Tx-1000[TI] OR Tx-500[TI] OR Wistran[TI] OR X-Tran[TI] OR Xamic [TI] OR aminocaproic[TI] OR aminohexanoic[TI] OR amino-caproic[TI] OR amino-n-hexanoic[TI] OR cy-116[TI] OR cy116[TI] OR lederle[TI] OR acikaprin[TI] OR afibrin[TI] OR amicar[TI] OR caprocid[TI] OR capracid[TI] OR capramol[TI] OR caprogel[TI] OR caprolest[TI] OR caprolisin[TI] OR caprolysin[TI] OR capromol[TI] OR epsikapron[TI] OR hemocaprol[TI] OR caproamin[TI] OR EACA[TI] OR caprolest[TI] OR capralense[TI] OR hexalense[TI] OR hamostat[TI] OR hemocid[TI] OR "cl 10304" [TI] OR cl10304[TI] OR ecapron[TI] OR ekaprol[TI] OR epsamon[TI] OR epsicaprom[TI] OR epsicapron[TI] OR epsilcapramin[TI] OR "epsilon amino caproate" [TI] OR "epsilon aminocaproate" [TI] OR epsilonaminocaproic[TI] OR epsilonaminocapronsav[TI] OR ethaaminocaproic[TI] OR ethaaminocaproic[TI] OR emocaprol[TI] OR hepin[TI] OR ip-silon[TI] OR jd177or neocaprol[TI] OR nsc26154[TI] OR resplamin[TI] OR tachostyptan[TI] OR aprotinin\* [TI] OR antagosan[TI] OR antilysin\* [TI] OR apronitin\* [TI] OR apronitrine[TI] OR aprotimbin[TI] OR aprotonin\* [TI] OR "bayer a 128" [TI] OR "bayer a128" [TI] OR contrical[TI] OR contrycal[TI] OR contrykal[TI] OR dilmintal[TI] OR "frey inhibitor" [TI] OR gordox[TI] OR haemoprot[TI] OR iniprol[TI] OR kontrikal[TI] OR kontrycal[TI] OR "Kunitz inhibitor" [TI] OR "Kunitz trypsin inhibitor" [TI] OR midran[TI] OR "pancreas antitrypsin" [TI] OR "pancreatic antitrypsin" [TI] OR protinin[TI] OR pulmin[TI] OR "riker 52g" [TI] OR rivilina[TI] OR "rp 9921" [TI] OR rp9921[TI] OR tracylol[TI] OR trascolan[TI] OR trasilol[TI] OR traskolan[TI] OR trasyolol[TI] OR trazylol[TI] OR "trypsin inhibitor" [TI] OR zymofren[TI] OR zymophren[TI])

#20 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 #7 AND #20

#22 (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] OR inprocess[sb]) NOT pubstatusnihms)

#23 #21 AND #22

## Appendix 6. Transfusion Evidence Library search strategy

TRANSFUSION EVIDENCE LIBRARY (1980 to 27 April 2016)

All Fields: (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology 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 (antifibrinolytics OR factor viia OR fibrinogen OR haemocomplettan OR platelet-poor plasma OR eltrombopag OR promacta OR revolade OR romiplastin OR romiplostim OR nplate OR thrombopoietin receptor agonist OR thrombopoietin agonist OR TPO OR interleukin OR sigosix OR neumega OR oprelvekin OR factor xiii OR factor xiiia OR fibrinase OR fxiii OR rfxiii OR fxiiia OR rfxiiia OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic)

## Appendix 7. LILACS search strategy

LILACS (1982 to 227 April 2016)

tw:(((haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology OR bone marrow failure OR bone marrow disease OR bone marrow disorder OR leukemia OR leukemia OR preleukemia OR preleukemia 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 (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 OR agonist OR TPO OR interleukin OR sigosix OR neumega OR oprelvekin OR factor xiii OR FXIII OR FXIIIa OR rFXIII OR rFXIIIa OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic) AND type of study:(clinical trials OR systematic reviews))) AND (instance:"regional") AND db:(LILACS)

## Appendix 8. INDMED search strategy

IndMed (1986 to 27 April 2016)

((factor viia OR rfviia OR rfviia OR fvii 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 OR interleukin OR IL-6 OR IL-11 OR sigosix OR neumega OR oprelvekin OR factor xiii OR factor xiiia OR FXIII OR FXIIIa OR rFXIII OR rFXIIIa OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic) AND (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology 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 (randomized OR randomised OR randomly OR blind OR blinded OR trial OR control group OR groups))

## Appendix 9. KOREAMED search strategy

KoreaMed (1997 to 27 April 2016)

“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 ALL] “Randomized Controlled Trial” [PT]  
Interleukin[ALL] AND “Randomized Controlled Trial” [PT]  
factor xiii[ALL] AND “Randomized Controlled Trial” [PT]  
tranexamic [ALL] AND “Randomized Controlled Trial” [PT]  
aprotinin [ALL] AND “Randomized Controlled Trial” [PT]  
aminocaproic [ALL] AND “Randomized Controlled Trial” [PT]  
EACA [ALL] AND “Randomized Controlled Trial” [PT]  
antifibrinolytic\*[ALL] AND “Randomized Controlled Trial” [PT]

## Appendix 10. Web of Science search strategy

Web of Science (Conference Proceedings Citation Index- Science (CPCI-S) - 1990 to 27 April 2016)

Topic: (antifibrinolytics OR “factor viia” OR “factor 7a” OR rfviia OR fvii 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 romiplostim OR romiplostim OR nplate OR “thrombopoietin receptor\*” OR “thrombopoietin agonist\*” OR “thrombopoietin mimetic\*” OR “interleukin 6” OR “interleukin 11” OR IL-6 OR IL-11 OR sigosix OR neumega OR oprelvekin OR “factor xiii” OR FXIII OR rFXIII OR FXIIIa OR RFXIIIa OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic)  
AND

Topic: (haematological OR hematological OR haematology OR hematology OR haemato-oncology OR hemato-oncology 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: (systematic\* OR random\* OR blind\* OR trial\* OR control\* OR groups)



## Appendix 11. ClinicalTrials.gov search strategy

ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/search>) to 27 April 2016

Search Terms: randomized OR randomised

Conditions: (hematological malignancies OR hemato-oncology OR bone marrow failure 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) AND

Interventions: (antifibrinolytics OR factor viia OR fibrinogen OR haemocomplettan OR platelet-poor plasma OR eltrombopag OR promacta OR revolade OR romiplostim OR romiplostim OR nplate OR thrombopoietin receptor agonist OR thrombopoietin agonist OR TPO OR interleukin 6 OR interleukin 11 OR IL-6 OR IL-11 OR sigosix OR neumega OR oprelvekin OR rhIL-11 OR factor xiii OR FXIII OR rFXIII OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic)

## Appendix 12. ICTRP search strategy

WHO International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) to 27 April 2016

Conditions: (marrow OR leukemia OR preleukemia OR anemia OR fanconi OR thrombocytopenia OR myelodysplasia OR hematological OR haematological OR hemato-oncological OR haemato-oncological OR myeloproliferative OR myelofibrosis OR myelosclerosis OR shwachman OR dyskeratosis OR dysmyelopoiesis)

AND

Intervention: (antifibrinolytics OR factor viia OR fvii OR rFvii OR novoseven 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 AMG531 OR AMG 531 OR thrombopoietin receptor agonist OR interleukin 6 OR interleukin 11 OR IL-6 OR IL-11 OR sigosix OR neumega OR oprelvekin OR rhIL-11 OR factor xiii OR FXIII OR rFXIII OR corifact OR fibrogammin OR tretten OR tranexamic OR aprotinin OR EACA OR aminocaproic)

## Appendix 13. Hong Kong Clinical Trials Registry search strategy

Hong Kong Clinical Trials Registry (<http://www.hkclinicaltrials.com/>) to 27 April 2016

Disease Group: Blood and blood-forming organs

Title: randomized OR randomised

## CONTRIBUTIONS OF AUTHORS

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

Andreas Hadjinicolaou: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis, and content expertise.

Anna Chaimani: protocol development, statistical expert and network meta-analysis expertise.

Marialena Trivella: protocol development and statistical expertise.

Paresh Vyas: protocol development and content expertise.

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

Sally Hopewell: protocol development and methodological expertise.

Simon Stanworth: protocol development and content expertise.

Lise Estcourt: protocol development and content expertise.

## DECLARATIONS OF INTEREST

Michael Desborough: none known.

Andreas Hadjinicolaou: none known.

Anna Chaimani: none known.

Mariakali Trivella: none known.

Paresh Vyas: none known.

Carolyn Doree: none known.

Sally Hopewell: none known.

Simon Stanworth: none known.

Lise Estcourt: none known.

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- National Institute for Health Research (NIHR) Cochrane Programme Grant, UK.  
To provide funding for systematic reviews and methodological support from the Centre for Statistics in Medicine, Oxford

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

### Outcomes not reported

The following outcomes were not reported but will be included in future updates of this review: days of bleeding per participant, platelet transfusion episodes, mean red cell transfusions per participant, red cell transfusion episodes, transfusion-transmitted infections, formation of antiplatelet antibodies or platelet refractoriness.

### Assessment of reporting bias

We would also draw contour-enhanced funnel plots to assess whether publication bias was likely to operate ([Peters 2008](#)). We would use a comparison-adjusted funnel plot and network meta-regression models to assess the presence of small-study effects in the entire network ([Chaimani 2012](#); [Chaimani 2013](#)).

### Combination of thrombopoietin mimetics

In addition to reporting individual results for romiplostim and eltrombopag, we have reported a pooled class effect for all types of thrombopoietin (TPO) mimetics.

## Methods for network meta-analysis

Network meta-analysis was not performed due to insufficient data. Network meta-analysis will be performed for future updates of this review. Full details are included in the published protocol for this review (Desborough 2016c). We planned to perform a network meta-analysis in Stata using the method of multivariate meta-analysis that treats the different comparisons in studies as different outcomes (StataCorp 2011; White 2012) and to perform this analysis using a network package with the mvmeta command (White 2011; White 2015), and present the results using the network graphs package in Stata (Chaimani 2013; Chaimani 2015).

## Time to event outcomes

For future updates of the review, if time-to-event outcomes are identified, we will employ the generic inverse variance method.

## Dealing with missing data

For future updates of the review, we will perform sensitivity analyses when possible to evaluate the robustness of results when we move away from the available-case analysis using the informative missingness parameter framework. We will use these analyses to account for the uncertainty imposed in the analyses due to the presence of missing outcome data (Mavridis 2014; White 2008). We will perform these analyses using the metamiss2 command in Stata available from <http://www.mtm.uoi.gr>.

## Measures and tests for heterogeneity

In network meta-analysis, we will assume a common estimate for the heterogeneity variance across the different comparisons. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ( $\tau^2$ ) estimated from the network meta-analysis models. For dichotomous outcomes, we will compare the magnitude of the heterogeneity variance with the empirical distribution. We will also estimate a total  $I^2$  value for heterogeneity in the network. The assessment of statistical heterogeneity in the entire network will be based on the magnitude of the heterogeneity variance parameter ( $\tau^2$ ) estimated from the network meta-analysis models. We will compare the magnitude of the heterogeneity variance with previously suggested empirical distributions (Rhodes 2015; Turner 2012). We will also estimate a total  $I^2$  value for heterogeneity in the network and estimated prediction intervals for all relative effects (Jackson 2014; Riley 2011). We will explore potential causes of heterogeneity by subgroup and meta-regression analyses when possible (Deeks 2011).

## Investigation of heterogeneity and inconsistency

### Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we plan to use the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop inconsistency factor. The magnitude of the inconsistency factors and their 95% CIs could be used to infer for the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. We will present the results of this approach graphically in a forest plot using the ifplot command of the network graphs package in Stata (StataCorp 2011).

### Global approaches for evaluating inconsistency

To evaluate the consistency assumption in the entire network simultaneously, we plan to use the design-by-treatment interaction model (Higgins 2012). This method accounts for two different sources of inconsistency that can occur when studies with different designs (for example, two-arm trials compared to three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we could infer the presence of inconsistency from any source in the entire network based on a Chi<sup>2</sup> test. We plan to perform the design-by-treatment model in Stata using the network package. Inconsistency and heterogeneity are interwoven; to distinguish between these two sources of variability, we will employ the  $I^2$  for inconsistency that measures the percentage of variability that could not be attributed to random error or heterogeneity (Jackson 2014).

### Subgroup analyses

If adequate data are available, we will perform subgroup analyses and network meta-regression for each of the following variables in order to explain heterogeneity, inconsistency or both.

- Type of bone marrow failure disorder (MDS, aplastic anaemia, myelofibrosis or congenital bone marrow failure disorder).
- Severity of disease.
- Baseline platelet count.
- Study precision.
- Assessment of transitivity across treatment groups.

### Transitivity

We will assess the assumption of transitivity by comparing the distribution of potential effect modifiers across different pairwise comparisons. In this context we expect the transitivity assumption to hold, assuming that the baseline characteristics of participants in each study are similar with regard to the severity of disease, baseline platelet count and co-interventions. We will evaluate epidemiologically the assumption of transitivity by comparing the clinical and methodological characteristics of sets of studies grouped by comparison ([Jansen 2013](#); [Salanti 2012](#)).

### Relative treatment ranking

We will obtain a hierarchy of the competing interventions using the surface area under the cumulative ranking curve (SUCRA) for primary outcomes and adverse events ([Salanti 2011](#)).

### Multi-arm trials

For future network meta-analysis, we will include all treatment arms from such studies and properly account for the correlation induced in the respective relative treatment effects.