Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation (Review)

Estcourt LJ, Stanworth SJ, Doree C, Hopewell S, Trivella M, Murphy MF



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[Intervention Review]

Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

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ABSTRACT

Background

Platelet transfusions are used in modern clinical practice to prevent and treat bleeding in people who are thrombocytopenic due to bone marrow failure. Although considerable advances have been made in platelet transfusion therapy in the last 40 years, some areas continue to provoke debate, especially concerning the use of prophylactic platelet transfusions for the prevention of thrombocytopenic bleeding.

This is an update of a Cochrane review first published in 2004, and previously updated in 2012 that addressed four separate questions: prophylactic versus therapeutic-only platelet transfusion policy; prophylactic platelet transfusion threshold; prophylactic platelet transfusion dose; and platelet transfusions compared to alternative treatments. This review has now been split into four smaller reviews looking at these questions individually; this review compares prophylactic platelet transfusion thresholds.

Objectives

To determine whether different platelet transfusion thresholds for administration of prophylactic platelet transfusions (platelet transfusions given to prevent bleeding) affect the efficacy and safety of prophylactic platelet transfusions in preventing bleeding in people with haematological disorders undergoing myelosuppressive chemotherapy or haematopoietic stem cell transplantation (HSCT).

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Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2015, Issue 6, 23 July 2015), MEDLINE (from 1946), Embase (from 1974), CINAHL (from 1937), the Transfusion Evidence Library (from 1950), and ongoing trial databases to 23 July 2015.

Selection criteria

We included RCTs involving transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given to prevent bleeding in people with haematological disorders (receiving myelosuppressive chemotherapy or undergoing HSCT) that compared different thresholds for administration of prophylactic platelet transfusions (low trigger (5 x 10^9/L); standard trigger (10 x 10^9/L); higher trigger (20 x 10^9/L, 30 x 10^9/L, 50 x 10^9/L); or alternative platelet trigger (for example platelet mass)).

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

Three trials met our predefined inclusion criteria and were included for analysis in the review (499 participants). All three trials compared a standard trigger (10 x 10^9/L) versus a higher trigger (20 x 10^9/L or 30 x 10^9/L). None of the trials compared a low trigger versus a standard trigger or an alternative platelet trigger. The trials were conducted between 1991 and 2001 and enrolled participants from fairly comparable patient populations.

The original review contained four trials (658 participants); in the previous update of this review we excluded one trial (159 participants) because fewer than 80% of participants had a haematological disorder. We identified no new trials in this update of the review.

Overall, the methodological quality of the studies was low across different outcomes according to GRADE methodology. None of the included studies were at low risk of bias in every domain, and all the included studies had some threats to validity.

Three studies reported the number of participants with at least one clinically significant bleeding episode within 30 days from the start of the study. There was no evidence of a difference in the number of participants with a clinically significant bleeding episode between the standard and higher trigger groups (three studies; 499 participants; risk ratio (RR) 1.35, 95% confidence interval (CI) 0.95 to 1.90; low-quality evidence).

One study reported the number of days with a clinically significant bleeding event (adjusted for repeated measures). There was no evidence of a difference in the number of days of bleeding per participant between the standard and higher trigger groups (one study; 255 participants; relative proportion of days with World Health Organization Grade 2 or worse bleeding (RR 1.71, 95% CI 0.84 to 3.48, P = 0.162; authors' own results; low-quality evidence).

Two studies reported the number of participants with severe or life-threatening bleeding. There was no evidence of any difference in the number of participants with severe or life-threatening bleeding between a standard trigger level and a higher trigger level (two studies; 421 participants; RR 0.99, 95% CI 0.52 to 1.88; low-quality evidence).

Only one study reported the time to first bleeding episode. There was no evidence of any difference in the time to the first bleeding episode between a standard trigger level and a higher trigger level (one study; 255 participants; hazard ratio 1.11, 95% CI 0.64 to 1.91; low-quality evidence).

Only one study reported on all-cause mortality within 30 days from the start of the study. There was no evidence of any difference in all-cause mortality between standard and higher trigger groups (one study; 255 participants; RR 1.78, 95% CI 0.83 to 3.81; low-quality evidence).

Three studies reported on the number of platelet transfusions per participant. Two studies reported on the mean number of platelet transfusions per participant. There was a significant reduction in the number of platelet transfusions per participant in the standard trigger group (two studies, mean difference -2.09, 95% CI -3.20 to -0.99; low-quality evidence).

One study reported on the number of transfusion reactions. There was no evidence to demonstrate any difference in transfusion reactions between the standard and higher trigger groups (one study; 79 participants; RR 0.07, 95% CI 0.00 to 1.09).

None of the studies reported on quality of life.

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Authors' conclusions

In people with haematological disorders who are thrombocytopenic due to myelosuppressive chemotherapy or HSCT, we found low-quality evidence that a standard trigger level (10 x 10^9/L) is associated with no increase in the risk of bleeding when compared to a higher trigger level (20 x 10^9/L or 30 x 10^9/L). There was low-quality evidence that a standard trigger level is associated with a decreased number of transfusion episodes when compared to a higher trigger level (20 x 10^9/L or 30 x 10^9/L).

Findings from this review were based on three studies and 499 participants. Without further evidence, it is reasonable to continue with the current practice of administering prophylactic platelet transfusions using the standard trigger level (10 x 10^9/L) in the absence of other risk factors for bleeding.

PLAIN LANGUAGE SUMMARY

Platelet transfusions are used to prevent bleeding in people with low platelet counts due to treatment-induced bone marrow failure

Review question

We evaluated the evidence about whether platelet transfusions given to prevent bleeding in people with lower platelet counts (for example 5 x 10^9/L or below) were as effective and safe as the current standard (10 x 10^9/L or below), or whether higher platelet count levels (20 x 10^9/L or below, 30 x 10^9/L or below, or 50 x 10^9/L or below) were safer than the current standard (10 x 10^9/L or below). Our target population was people with blood cancers (for example leukaemia, lymphoma, myeloma) who were receiving intensive (myelosuppressive) chemotherapy treatments or stem cell transplantation.

Background

People with blood cancers may have low platelet counts due to their underlying cancer. Blood cancers may be treated with chemotherapy and stem cell transplantation, and these treatments can cause low platelet counts. Platelet transfusions may be given to prevent bleeding when the platelet count falls below a prespecified threshold platelet count (for example 10 x 10^9/L), or may be given to treat bleeding (such as a prolonged nosebleed or multiple bruises). Giving platelet transfusions at a lower prespecified threshold platelet count may increase the chance that bleeding will occur, which may be harmful, whereas giving platelet transfusions at a higher prespecified threshold platelet count may mean that people receive unnecessary platelet transfusions. Platelet transfusions can have adverse effects and have cost and resource implications for health services, so unnecessary transfusions should be avoided.

Study characteristics

The evidence is current to July 2015. We found no new studies in this update of the review. This review identified three randomised controlled trials that compared giving platelet transfusions to prevent bleeding when the platelet count is 10 x 10^9/L (the current standard) or below versus giving platelet transfusions to prevent bleeding at higher platelet count levels (20 x 10^9/L or below or 30 x 10^9/L or below). None of the studies compared a lower trigger or alternative trigger to the current standard. These trials were conducted between 1991 and 2001 and included 499 participants. Two trials included adults with leukaemia who were receiving chemotherapy. One trial included children and adults receiving a stem cell transplant.

Two of the three studies reported sources of funding. Neither of the studies that reported funding sources were industry sponsored.

Key results

Giving platelet transfusions to people with low platelet counts due to blood cancers or their treatment to prevent bleeding when the platelet count was 10 x 10^9/L or below did not increase the risk of bleeding compared to giving a platelet transfusion at higher platelet counts (20 x 10^9/L or below or 30 x 10^9/L or below).

Giving platelet transfusions to prevent bleeding only when the platelet count was 10 x 10^9/L or below resulted in a reduction in the number of platelets given. We found no evidence to demonstrate that giving a platelet transfusion when the platelet count was 10 x 10^9/L or below decreased the number of transfusion reactions compared to giving platelet transfusions at higher platelet counts (20 x 10^9/L or below or 30 x 10^9/L or below).

None of the three studies reported any quality of life outcomes.

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Findings from this review were based on three studies and 499 participants. Without further evidence, it is reasonable to continue using platelet transfusions to prevent bleeding based on the current standard transfusion threshold (10 x 10^9/L).

Quality of the evidence

The evidence for most of the findings was of low quality. This was because participants and their doctors knew which study arm the participant had been allocated to, and also the estimate of the treatment effect was imprecise.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Prophylactic platelet transfusion at threshold of 10,000 compared to higher transfusion threshold (20,000 or 30,000) for prevention of haemorrhage after chemotherapy and stem cell transplantation

Patient or population: People with a haematological disorder
Settings: Receiving intensive chemotherapy or a stem cell transplant
Intervention: Prophylactic platelet transfusion at threshold of 10 x 10^9/L
Comparison: Higher transfusion threshold (20 x 10^9/L or 30 x 10^9/L)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Higher transfusion threshold (20 x 10^9/L or 30 x 10^9/L)	Prophylactic platelet transfusion at threshold of 10 x 10^9/L				
Numbers of participants with at least 1 clinically significant bleeding event up to 30 days from study entry	**177 per 1000**	**239 per 1000** (168 to 336)	**RR 1.35** (0.95 to 1.9)	499 (3 studies)	⊕⊕◯◯ **low**[1,2]	The definition of clinically significant bleeding varied between studies, because there were differences in the way bleeding was graded
Number of days on which clinically significant bleeding occurred per participant up to 30 days from study entry	Not estimable[3]	Not estimable[3]	Not estimable[3]	255 (1 study)	⊕⊕◯◯ **low**[1,2]	-
Number of participants with WHO Grade 3 or 4 bleeding up to 30 days from study entry	**82 per 1000**	**81 per 1000** (43 to 154)	**RR 0.99** (0.52 to 1.88)	421 (2 studies)	⊕⊕◯◯ **low**[1,2]	-

Time to first bleeding episode (days)	-	-	**HR 1.11** (0.64 to 1.91)	255 (1 study)	⊕⊕◯◯ **low**[1,2]	-
Number of platelet transfusions per participant up to 30 days from study entry	The mean number of platelet transfusions per participant in the 10 x 10^9/L group was **2.09 lower** (3.2 to 0.99 lower)		-	333 (2 studies)	⊕⊕◯◯ **low**[1,2]	-
Mortality from all causes up to 30 days from study entry	**75 per 1000**	**134 per 1000** (62 to 286)	**RR 1.78** (0.83 to 3.81)	255 (1 study)	⊕⊕◯◯ **low**[1,2]	-
Quality of life - not reported	Not estimable	Not estimable	Not estimable	-	See comment	None of the studies reported quality of life

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **HR:** Hazard ratio; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]The number of participants from all three studies may not be large enough to detect a clinically significant difference. The confidence intervals are wide, and therefore there is uncertainty about the result. The level of evidence was downgraded by 1 due to imprecision.
[2]All of the studies were at high risk of bias due to lack of blinding and more protocol deviations in the standard-trigger arm (10 x 10^9/L). The Rebulla study did not perform an intention-to-treat analysis and excluded 2 participants who died within 24 hours of entering the study. The level of evidence was downgraded by 1 due to risk of bias.
[3]The authors of Rebulla 1997 reported a relative proportion of days with WHO Grade 2 or worse bleeding of 1.71 (95% CI 0.84 to 3.48) for the standard versus higher transfusion trigger arms. A permutation test for the comparison of these proportions gives a P value of 0.162, and therefore no significant difference between study arms was found. These results are the authors' own results.

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BACKGROUND

Description of the condition

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

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

People can become refractory to platelet transfusions. In an analysis of the TRAP 1997 study data, there was a progressive decrease in the post-transfusion platelet count increments and time interval between transfusions as the number of preceding transfusions increased (Slichter 2005). This effect was seen irrespective of whether or not participants had developed detectable human leukocyte antigen (HLA) antibodies (Slichter 2005).

Platelet transfusions are also associated with adverse events. Mild to moderate reactions to platelet transfusions include rigors, fever, and urticaria (Heddle 2009b). Although these reactions are not life-threatening, they can be extremely distressing for the patient. Rarer but more serious sequelae include anaphylaxis, transfusion-transmitted infections, transfusion-related acute lung injury, and immunomodulatory effects (Benson 2009; Blumberg 2009; Bolton-Maggs 2012; Heddle 2009b; Knowles 2011; Pearce 2011; Popovsky 1985; Silliman 2003; Taylor 2010).

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

Description of the intervention

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

Prophylactic platelet transfusion threshold

Prophylactic platelet transfusions are typically given when blood platelet counts fall below a given trigger level. Studies have compared different platelet count thresholds to trigger the administration of prophylactic platelet transfusions. The current consensus is that people should receive a platelet transfusion when the platelet count is less than 10 x 10^9/L, unless there are other risk factors for bleeding such as sepsis, concurrent use of antibiotics, or other abnormalities of haemostasis (BCSH 2003; BCSH 2004; Board 2009; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007). The experimental interventions were higher or lower platelet transfusion thresholds.

The previous review raised the issue that a platelet count of 10 x 10^9/L may not be equivalent to 20 x 10^9/L as previously thought (Estcourt 2012a).

How the intervention might work

Prophylactic platelet threshold

The morning platelet count has traditionally been used to indicate when a patient requires prophylactic platelet transfusions. It became standard practice to transfuse platelets at platelet counts

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below 20 x 10^9/L, in an attempt to prevent bleeding (Beutler 1993). This practice was partly based on the findings of non-randomised studies that showed that gross haemorrhage (haematuria, haematemesis, and melaena) was present at platelet counts below 5 x 10^9/L more frequently than when the platelet count was between 5 x 10^9/L and 100 x 10^9/L (Gaydos 1962; Slichter 1978). However, these studies did not clearly support the use of a threshold for prophylactic platelet transfusion of 20 x 10^9/L, nor was any threshold effect seen (Gaydos 1962; Slichter 1978). A similar pattern of increased bleeding at platelet counts $\leq$ 5 x 10^9/L was also seen in two recent RCTs (Slichter 2010; Wandt 2012).

The routine use of platelet transfusions in people with haematological malignancies from the 1970s resulted in a decreased mortality rate due to bleeding (less than 1% of patients) (Slichter 1980). Despite the lack of evidence, the widespread use of a threshold platelet count of 20 x 10^9/L for prophylactic platelet transfusions led to a marked growth in the demand for platelet concentrates (Sullivan 2002). This increased demand stimulated research to address whether the threshold could be safely lowered to 10 x 10^9/L (Rebulla 1997, reviewed in Stanworth 2004). The consensus formulated from these trials was that people should receive a platelet transfusion when the platelet count is < 10 x 10^9/L, unless there are other risk factors for bleeding such as sepsis, concurrent use of antibiotics, or other abnormalities of haemostasis (BCSH 2003; BCSH 2004; Board 2009; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007), when the threshold should be raised.

There have been calls for a further reduction in the threshold to 5 x 10^9/L because of the previously mentioned evidence for an increased rate of bleeding at a platelet count of $\leq$ 5 x 10^9/L (BCSH 2003; Gmür 1991). However, a major concern in doing this is the reported inaccuracy of current automated counters when the platelet count is very low (Harrison 2001). This was well demonstrated in a large multi-centre study of platelet analyser accuracy when measuring platelet counts < 20 x 10^9/L (Segal 2005).

Platelet mass has been used as a transfusion trigger for neonatal platelet transfusions (Gerday 2009). Different platelet count thresholds have been the only known trigger used in people with a haematological disorder.

Assessment of bleeding

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

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

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

The majority of trials have used the WHO system, or a modification of it, for grading bleeding (Estcourt 2013; Koreth 2004; WHO 1979). One limitation of all the scoring systems based on the WHO system is that the categories are relatively broad and subjective, meaning that a small change in a participant's bleeding risk may not be detected. Another limitation is that the modified WHO categories are partially defined by whether a bleeding participant requires a blood transfusion. The threshold for intervention may vary between clinicians and institutions, and so the same level of bleeding may be graded differently in different institutions.

The definition of what constitutes clinically significant bleeding has varied between studies. Although the majority of more recent platelet transfusion studies have classified it as WHO Grade 2 or above (Heddle 2009a; Slichter 2010; Stanworth 2010; Wandt 2012), in the past there has been greater heterogeneity (Cook 2004; Estcourt 2013; Koreth 2004). The difficulties of assessing and grading bleeding may limit the ability to compare results between studies, and this needs to be kept in mind when reviewing the evidence for the effectiveness of prophylactic platelet transfusions at different doses.

Why it is important to do this review

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

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

The initial formulation of this Cochrane review attempted to answer these questions, but the evidence at the time was insufficient for us to draw any definitive conclusions (Stanworth 2004). This review was updated (Estcourt 2012a). For clarity and simplicity, we have now split the review to answer each question separately. This review focuses solely on the second question: Which threshold should be used to trigger the transfusion of prophylactic platelets?

Avoiding the need for unnecessary prophylactic platelet transfusions in people with haematological disorders will have significant logistical and financial implications for national health services as well as decreasing patients' exposure to the risks of transfusion. These factors are perhaps even more important in the development of platelet transfusion strategies in low-income countries, where

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access to blood components is much more limited than in high-income countries (Verma 2009).

This review did not assess the evidence for the answers to the other two questions, as these are the focus of separate Cochrane reviews, nor did it assess the use of alternative agents instead of prophylactic platelet transfusions because this is the focus of another review.

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

OBJECTIVES

To determine whether different platelet transfusion thresholds for administration of prophylactic platelet transfusions (platelet transfusions given to prevent bleeding) affect the efficacy and safety of prophylactic platelet transfusions in preventing bleeding in people with haematological disorders undergoing myelosuppressive chemotherapy or haematopoietic stem cell transplantation (HSCT).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in this review irrespective of language or publication status.

Types of participants

People with haematological disorders receiving treatment with myelosuppressive chemotherapy or stem cell transplantation, or both. We included people of all ages, in both inpatient and outpatient clinical settings. If trials consisted of mixed populations of patients (for example people with diagnoses of solid tumours), we used only data from the haematological subgroups. If subgroup data for haematological patients were not provided (after contacting the authors of the trial), we excluded the trial if fewer than 80% of participants had a haematological disorder. We excluded any participants who were not being treated with intensive chemotherapy or a stem cell transplant. We included participants with non-malignant haematological disorders (for example aplastic anaemia, congenital bone marrow failure syndromes) who were being treated with an allogeneic stem cell transplant. These participants would be expected to be thrombocytopenic during pre-transplant conditioning therapy and during the transplantation period, requiring platelet transfusion support.

Types of interventions

Participants received transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given prophylactically to prevent bleeding. Prophylactic platelet transfusions are typically given when blood platelet counts fall below a given trigger level. There was no restriction on dose or frequency of platelet transfusion or the type of platelet component, but we took this information into account in the analysis, where available.

We included the following comparisons:

- Lower platelet count threshold (5 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L).
- Higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L).
- Different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that do not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L).
- Alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number). As there are currently no standard thresholds used for these alternative platelet measures, we planned to use the study's own thresholds for these alternative measures.

Types of outcome measures

Primary outcomes

Number and severity of bleeding episodes during the first 30 days of the study:

1. The number of participants with at least one bleeding episode.
2. The total number of days on which bleeding occurred.
3. Number of participants with at least one episode of severe or life-threatening haemorrhage.
4. Time to first bleeding episode from the start of study.

Secondary outcomes

1. Mortality (all-causes, secondary to bleeding, and secondary to infection) within 30 and 90 days from the start of the study.
2. Number of platelet transfusions per participant and number of platelet components per participant within 30 days from the start of the study.

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3. Number of red cell transfusions per participant and number of red cell components per participant within 30 days from the start of the study.

4. Platelet transfusion interval within 30 days from the start of the study.

5. Proportion of participants requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate).

6. Overall survival within 30, 90, and 180 days from the start of the study.

7. Proportion of participants achieving complete remission within 30 and 90 days from the start of the study.

8. Total time in hospital within 30 days from the start of the study.

9. Adverse effects of treatments (transfusion reactions, thromboembolism, transfusion-transmitted infection, development of platelet antibodies, development of platelet refractoriness) within 30 days from the start of the study.

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

We expressed all primary and secondary outcomes in the formats defined in the Measures of treatment effect section of this protocol if data were available, except for two of our outcomes that we planned to be only narrative reports.

These were:

- Platelet transfusion interval, as it can be calculated in many different ways and it was unlikely that the exact methodology would be reported sufficiently to allow us to combine the data.
- Assessment of quality of life (QoL). We planned to use the study's own measure, as there is no definitive patient-reported outcome measure for this patient group (Estcourt 2014e).

However, none of the included studies reported either of these outcomes.

Search methods for identification of studies

The Systematic Review Initiative (SRI) Information Specialist (CD) formulated new search strategies in collaboration with the Cochrane Haematological Malignancies Review Group based on those used in previous versions of this review (Estcourt 2012a; Stanworth 2004).

Electronic searches

Bibliographic databases

We searched for RCTs in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2015, Issue 6, 23 July 2015) (Appendix 1)
- MEDLINE (OvidSP, 1946 to 23 July 2015) (Appendix 2)
- PubMed (epublications only to 23 July 2015) (Appendix 3)
- Embase (OvidSp, 1974 to the 23 July 2015) (Appendix 4)
- CINAHL (EBSCOhost, 1937 to 23 July 2015) (Appendix 5)
- UKBTS/SRI Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to 23 July 2015) (Appendix 6)
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 23 July 2015) (Appendix 7)
- LILACS (BIREME/PAHO/WHO, 1982 to to 23 July 2015) (Appendix 8)
- IndMed (ICMR-NIC, 1985 to 23 July 2015) (Appendix 9)
- KoreaMed (KAMJE, 1997 to 23 July 2015) (Appendix 10)
- PakMediNet (2001 to 23 July 2015) (Appendix 10)

We updated searches from the original search in January 2002, Stanworth 2004, and the updated search on 10 November 2011 (Estcourt 2012a). We combined searches in MEDLINE, Embase, and CINAHL with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We did not limit searches by language or publication status.

Databases of ongoing trials

We also searched ClinicalTrials.gov (http://clinicaltrials.gov/ct2/search) (Appendix 11), the WHO International Clinical Trials Registry (ICTRP) (http://apps.who.int/trialsearch/) (Appendix 11), the ISRCTN Register (http://www.controlled-trials.com/isrctn/) (Appendix 12), the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search) (Appendix 12), and the Hong Kong Clinical Trials Register (http://www.hkclinicaltrials.com/) (Appendix 13) in order to identify ongoing trials to 23 July 2015.

All new search strategies are presented as indicated in Appendices 1 to 13. Search strategies for both the original (2002) and update (2011) searches are presented in Appendix 14.

Searching other resources

We augmented database searching with the following.

Handsearching of reference lists

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

Personal contacts

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

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Data collection and analysis

Selection of studies

We updated the selection of studies from the selection of studies performed for the previous version of this review (Estcourt 2012a). Two out of three independent review authors (LE, PB, and CD) initially screened all electronically derived citations and abstracts of papers identified by the review search strategy for relevance. We excluded studies clearly irrelevant at this stage.

Two independent review authors (LE, PB) then formally assessed the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We resolved all disagreements by discussion without the need to consult a third review author (SS). We sought further information from study authors if an article contained insufficient data to make a decision about eligibility. We designed a study eligibility form for trials of platelet transfusion to help in the assessment of relevance, which included ascertaining whether the participants had haematological disorders and whether the two groups could be defined in the trial on the basis of differences in use of prophylactic platelet transfusion doses. We recorded the reasons why potentially relevant studies failed to meet the eligibility criteria.

Data extraction and management

We updated the data extraction from the data extraction performed for the previous version of this review, Estcourt 2012a, to include new review outcomes that were not part of the previous review (for example platelet transfusion interval, quality of life). We identified no new studies in this updated review.

Two review authors (LE, SS) conducted data extraction according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011a). Any disagreements between the review authors were resolved by consensus. The review authors were not blinded to names of authors, institutions, journals, or the outcomes of the trials. The data extraction forms had been piloted in the previous version of this review (Estcourt 2012a). Due to minor changes in the format, we piloted the forms on a further study; thereafter the two review authors (LE, SS) independently extracted data for all the studies. We extracted the following data.

General information

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

Trial details

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

Characteristics of participants

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

Interventions

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

Assessment of bias

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

Outcomes measured

Number and severity of bleeding episodes. Mortality (all causes), and mortality due to bleeding. Overall survival. Proportion of participants achieving complete remission. Time in hospital. Number of platelet transfusions and platelet components. Number of red cell transfusions and red cell components. Platelet transfusion interval. Proportion of participants requiring additional interventions to stop bleeding (surgical, medical such as tranexamic acid, other blood products such as fresh frozen plasma (FFP), cryoprecipitate). Quality of life. Adverse effects of treatments (for example transfusion reactions, thromboembolism, transfusion-transmitted infection, development of platelet antibodies or platelet refractoriness).

We used both full-text versions and abstracts to retrieve the data. We extracted publications reporting on more than one trial using one data extraction form for each trial. We extracted trials reported in more than one publication on one form only. When these sources provided insufficient information, we contacted the authors and study groups for additional details.

One review author performed data entry into software, which a second review author checked for accuracy.

Assessment of risk of bias in included studies

We updated the 'Risk of bias' assessment to include study funding from the 'Risk of bias' assessment performed for the previous version of this review (Estcourt 2012a).

The assessment included information about the design, conduct, and analysis of the trial. We evaluated each criterion on a three-

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point scale: low risk of bias, high risk of bias, or unclear (Higgins 2011c). To assess risk of bias, we addressed the following questions in the 'Risk of bias' table for each included study:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study (including an assessment of blinding of participants, personnel, and outcome assessors)?
- Were incomplete outcome data adequately addressed (for every outcome separately)?
- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias? This included assessing whether protocol deviation was balanced between treatment arms.

Measures of treatment effect

For dichotomous outcomes, we recorded the number of outcomes in the treatment and control groups and estimated the treatment effect measures across individual studies as the relative effect measures (risk ratio with 95% confidence intervals (CIs)).

For continuous outcomes, we recorded the mean and standard deviations. For continuous outcomes measured using the same scale, the effect measure was the mean difference with 95% CIs, or the standardised mean difference for outcomes measured using different scales. For time-to-event outcomes, we extracted the hazard ratio from published data according to Parmar 1998 and Tierney 2007.

We did not report the number needed to treat to benefit with CIs and the number needed to treat to harm with CIs because there were no differences between any of the bleeding outcomes.

If we could not report the available data in any of the formats described above, we performed a narrative report.

Unit of analysis issues

We did not prespecify in the protocol how we would deal with any unit of analysis issues. There was a unit of analysis issue for this review for the total number of days of bleeding. We only reported the number of days of bleeding if it had been reported per participant or if an appropriate analysis had been performed by the authors to account for repeated measures. In this review, the Rebulla 1997 authors used a permutation analysis to take into account the repeated events data (Freedman 1989). All other studies had not taken into account unit of analysis issues with this outcome and data were not reported.

Dealing with missing data

We dealt with missing data according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We contacted four authors to obtain information that was missing or unclear in the published report. Two authors supplied missing data (Heckman 1997; Rebulla 1997).

In trials that included people with haematological disorders as well as people with solid tumours or non-malignant haematological disorders, we extracted data for the malignant haematology subgroup from the general trial data. We could not do this in one study (Zumberg 2002); we contacted the authors, but they no longer had access to the original data, and the original reports did not provide subgroup data. We therefore excluded this study from the review.

Within an outcome, the preferred analysis was an intention-to-treat analysis. When data were missing, we recorded the number of participants lost to follow-up for each trial.

Assessment of heterogeneity

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

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias (small-trial bias) because we included only three studies in this review (Sterne 2011).

Data synthesis

We performed analyses according to the recommendations of The Cochrane Collaboration (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into Review Manager 5.3.

Where meta-analysis was feasible, we used the fixed-effect model for pooling the data. We used the Mantel-Haenszel method for dichotomous outcomes, and the inverse-variance method for continuous outcomes. We used the generic inverse-variance method for time-to-event outcomes.

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

Summary of findings tables

We used GRADE 2014 to create 'Summary of findings' tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). This included the number and severity of bleeding episodes within 30 days from the start of the study (number of participants with at least one bleeding episode;

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number of days on which bleeding occurred; number of participants with severe or life-threatening bleeding; time to first bleeding episode), number of platelet transfusions within 30 days from the start of the study, 30-day mortality, and quality of life.

Subgroup analysis and investigation of heterogeneity

We considered performing subgroup analysis on the following characteristics, if appropriate:

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

We did not perform two subgroup analyses due to lack of data; these were presence of fever and type of treatment.
We did not perform meta-regression because no subgroup contained more than 10 studies (Deeks 2011). We commented on differences between subgroups as a narrative.
Investigation of heterogeneity between studies also included, if appropriate:

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

We did not assess age of study as a reason for heterogeneity, as all studies recruited participants between 1991 and 2001.

Sensitivity analysis

We had intended to assess the robustness of our findings by the following two sensitivity analyses:

- Including only those trials at low risk of bias.
- Including only those trials in which 20% of participants or less were lost to follow-up.

All trials were at risk of bias because none of the three included RCTs blinded investigators to the intervention.
None of the three included trials had more than 20% of participants lost to follow-up.
We therefore did not perform these two pre-planned sensitivity analyses.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies; there were no ongoing studies.

Results of the search

See PRISMA flow diagram (Figure 1).

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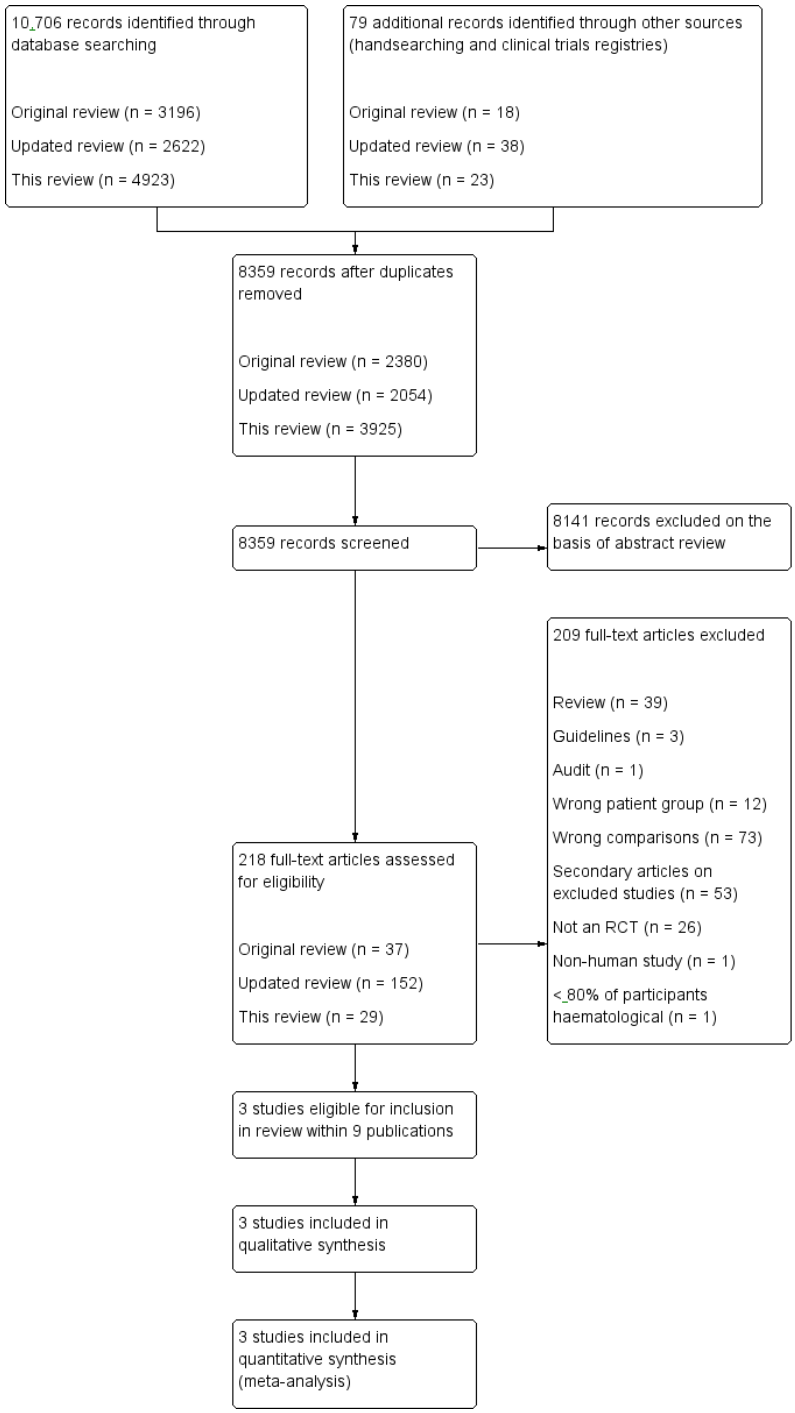
Figure 1. Study flow diagram.



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The original search (conducted January 2002) identified a total of 3196 potentially relevant records. There were 2380 records after duplicates were removed, and 2343 records were excluded on the basis of the abstract. The original systematic review identified 37 studies that appeared relevant on the basis of their full text or abstract using the original inclusion/exclusion criteria (Stanworth 2004).This was performed by one review author.
The updated search for the previous review (conducted November 2011) identified a total of 2622 potentially relevant records. There were 2054 records after duplicates were removed, and two review authors excluded 1865 records on the basis of the abstract. We retrieved 152 full-text articles for relevance. Two review authors (LE, SS) reviewed these full-text articles and those from the original review (a total of 189 records) (Estcourt 2012a).
The latest update of the search (conducted 23 July 2015) identified a total of 4923 potentially relevant records. There were 3925 records after duplicates were removed. Two review authors (LE, SS) were able to exclude 3896 records on the basis of the abstract. Two review authors (LE, SS) retrieved for relevance and reviewed 29 full-text articles.

Included studies

See Characteristics of included studies for full details of each study.

Ongoing studies

This update of the review identified no ongoing studies that were eligible for inclusion.

Studies contributing to the main outcome

The three RCTs (9 publications) were published between 1997 and 2005. There were six secondary citations of included studies (cited as secondary references for the relevant included studies). There were no new studies. The three included studies, Diedrich 2005, Heckman 1997, and Rebulla 1997, were identified in the previous version of this review (Estcourt 2012a). One study that had been included in the original review, Stanworth 2004, was excluded in the previous version of this review, Estcourt 2012a, because fewer than 80% of participants had a haematological disorder, and no subgroup data could be identified (Zumberg 2002). The three included RCTs were distributed across the review's four subcategories as follows:

- No studies compared a lower platelet count threshold (5 x 10^9/L) versus a standard platelet transfusion threshold (10 x 10^9/L).
- All three studies compared a standard platelet transfusion threshold (10 x 10^9/L) versus a higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L).
- No studies compared different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L).
- No studies compared alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number).

This review therefore only discussed the subcategory that compared a standard platelet transfusion threshold (10 x 10^9/L) versus a higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L).
See Table 1 for study characteristics including: number and type of participants; type of intervention (actual thresholds used); duration of study; dose of platelet component; type of platelet product; and primary outcome.

Study design

All three studies were open-label studies. Two studies were single-centre parallel RCTs (Diedrich 2005; Heckman 1997), and one study was a multicentre parallel RCT (Rebulla 1997).

Study size

The number of participants randomised ranged from 78 in Heckman 1997 to 276 in Rebulla 1997.

Setting

Two studies were conducted in the 1990s (Heckman 1997; Rebulla 1997), and one study was conducted in the early 2000s (Diedrich 2005). The studies were conducted in Italy (Rebulla 1997), Sweden (Diedrich 2005), and the United States (Heckman 1997).

Participants

In total, 520 participants were randomised; of these, 499 were included in the analysis. We excluded 21 participants randomised in Rebulla 1997 from the analysis (16 no study records received; two received non-myeloablative chemotherapy; three died (two within 24 hours of enrolment in the study). Two of the studies examined adults with acute leukaemia; one included adults with acute lymphocytic leukaemia (ALL) or acute myeloid leukaemia (AML) (Heckman 1997), and the other included only adults with AML (Rebulla 1997). Both studies excluded adults with acute promyelocytic leukaemia (APL). The third study included both adults and children undergoing an allogeneic HSCT (Diedrich 2005).

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Intervention

Two studies compared a prophylactic transfusion threshold of 10 x 10^9/L with a threshold of 20 x 10^9/L (Heckman 1997; Rebulla 1997). One study compared a threshold of 10 x 10^9/L with a threshold of 30 x 10^9/L (Diedrich 2005).

Co-interventions

In two of the three studies a red cell transfusion policy was stated (Diedrich 2005; Rebulla 1997). Both studies transfused red cells when the haemoglobin was less than 80 g/L.

Outcomes

Two of the three studies defined a primary outcome (Diedrich 2005; Rebulla 1997). In Rebulla 1997, the primary outcome was the frequency and severity of bleeding, and the secondary outcome was the number of platelet transfusions, whereas in Diedrich 2005, the number of platelet transfusions was the primary outcome, with bleeding as one of the secondary outcomes. The third study, Heckman 1997, stated that its main aims were to look at platelet use and bleeding complications. All three studies commented on adverse events associated with platelet transfusions.

Funding sources

Two studies reported the funding sources for the trial (Diedrich 2005; Heckman 1997). All funding sources were either charitable foundations or government funds.

Excluded studies

See Characteristics of excluded studies for further details.

- Twelve studies were excluded because they compared different participant groups (Andrew 1993; Arnold 2006; Bai 2004; Fanning 1995; Gajic 2006; Gerday 2009; Johansson 2007; Julmy 2009; NCT00699621; Reed 1986; Spiess 2004; Vadhan-Raj 2002).
- Seventy-three studies compared different types of platelet formulations with outcome measures not relevant to the eligibility criteria (Agliastro 2006; Akkök 2007; Anderson 1997; Arnold 2004; Bentley 2000; Blumberg 2002; Blumberg 2004; Blundell 1996; Carr 1990; Corash 2001; Couban 2002; de Wildt-Eggen 2000; Diedrich 2009; Di Pietro 1998; Dumont 2011; Gmür 1983; Goodnough 2001; Goodrich 2008; Grossman 1980; Gurkan 2007; Harrup 1999; Heal 1993; Heddle 1994; Heddle 1999; Heddle 2002; Heddle 2005; Heddle 2009; Higby 1974; ISRCTN01292427; ISRCTN49080246; ISRCTN56366401; Kakaiya 1981; Kerkhoffs 2010; Klumpp 1999; Kluter 1996; Lapierre 2003; Leach 1991; Lee 1989; Lozano 2010; Lozano 2011; Lu 2011; McCullough 2004; Messerschmidt 1988; Mirasol 2010; Murphy 1982; Murphy 1986; NCT01615146; Norville 1994; Norville 1997; Oksanen 1991; Oksanen 1994; Pamphilon 1996; Schiffer 1983; Shanwell 1992; Singer 1988; Sintnicolaas 1981; Sintnicolaas 1982; Sintnicolaas 1995; Slichter 1998; Slichter 2006; Slichter 2010; Solomon 1978; Stanworth 2013; Strindberg 1996; Sweeney 2000; Tinmouth 2004; TRAP 1997; Van Marwijk 1991; van Rhenen 2003; Wandt 2012; Wang 2002; Williamson 1994; Zhao 2002).
- Three records were guidelines (Follea 2004; Samama 2005; Tosetto 2009).
- One record was an audit (Qureshi 2007).
- Thirty-nine records were reviews (Andreu 2009; Avvisati 2003; Benjamin 2002; Blajchman 2008; Buhrkuhl 2010; Casbard 2004; Cid 2007; Dzik 2004; Goodnough 2002; Goodnough 2005; Heal 2004; Heddle 2003; Heddle 2007; Jelic 2006; Levi 2002; Lordkipanidze 2009; Lozano 2003; Martel 2004; McNicol 2003; Paramo 2004; Poon 2003; Rabinowitz 2010; Rayment 2005; Razzaghi 2012; Roberts 2003; Sakakura 2003; Shehata 2009; Shen 2007; Slichter 2004; Slichter 2007; Slichter 2012; Sosa 2003; Strauss 2004; Strauss 2005; Tinmouth 2003; Wandt 2010; Wang 2005; Woodard 2002; Zeller 2014).
- Twenty-six studies were not RCTs (Aderka 1986; Callow 2002; Cameron 2007; Chaoui 2005; Chaurasia 2012; Decaudin 2004; Eder 2007; Elting 2002; Elting 2003; Friedmann 2002; Gil-Fernandez 1996; Gmür 1991; Greeno 2007; Hardan 1994; Lawrence 2001; Navarro 1998; Nevo 2007; Norol 1998; Paananen 2009; Sagmeister 1999; Verma 2008; Wandt 1998; Wandt 2005; Wandt 2006; Weigand 2009; Zahur 2002).
- Fifty-three records were secondary citations of excluded studies (cited as secondary references for the relevant excluded studies).
- One study was a non-human study (Velik-Salchner 2007).
- One study was a study in which fewer than 80% of the participants were haematological patients, and no data were available on the haematological subgroup (Zumberg 2002). Zumberg 2002 had been included in the previous review Stanworth 2004, but for this reason it has now been excluded.

Risk of bias in included studies

See Figure 2 and Figure 3 for visual representations of the 'Risk of bias' assessments across all studies and for each item in the included studies. See the Characteristics of included studies section 'Risk of bias' table for further information about the bias identified within the individual trials.

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

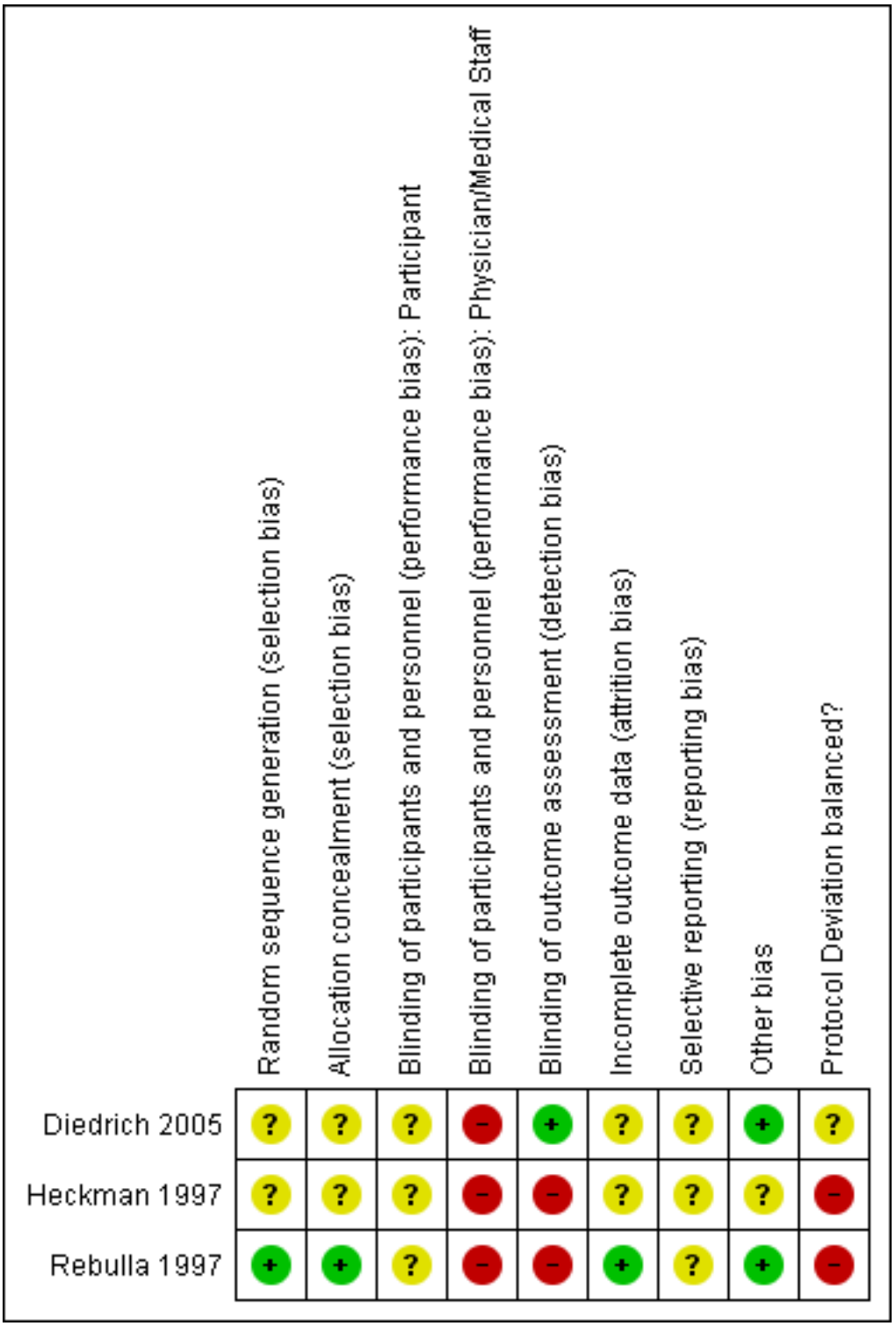

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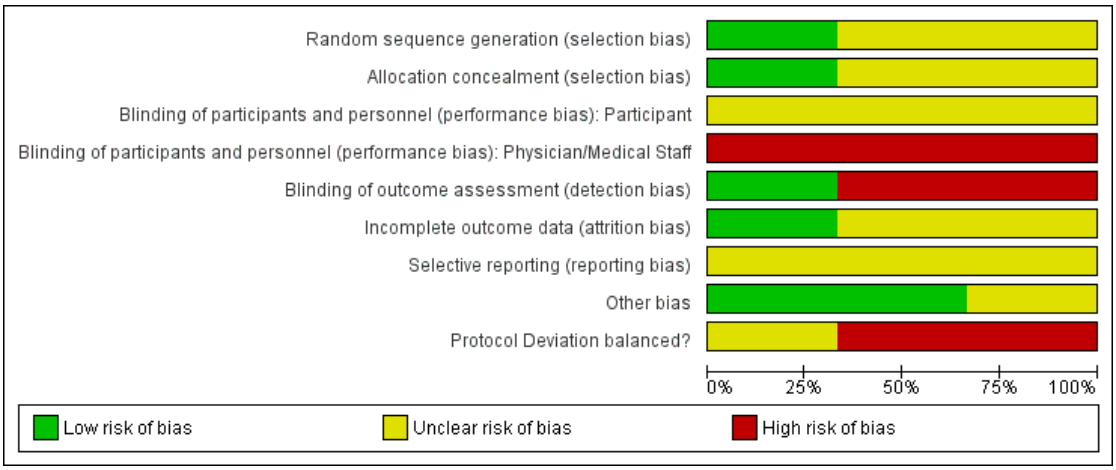
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



All three studies had some threats to validity (Diedrich 2005; Heckman 1997; Rebulla 1997). The majority of these potential risks were due to a lack of detail provided on the specific criteria and were thus judged as 'unclear risk' using the Cochrane grading system.

Allocation

We assessed one study as low risk of selection bias due to adequate methods of sequence generation and allocation concealment (Rebulla 1997). We assessed the two remaining studies as unclear risk of selection bias due to the lack of information on sequence generation and allocation concealment (Diedrich 2005; Heckman 1997).

Blinding

We assessed all three studies as high risk of performance bias due to lack of blinding of medical staff (Diedrich 2005; Heckman 1997; Rebulla 1997).

We assessed one study as low risk of detection bias because there was adequate blinding of the bleeding assessor (Diedrich 2005). We assessed the other two studies as high risk of detection bias because the bleeding assessors and medical staff were unblinded (Heckman 1997; unpublished data of Rebulla 1997).

Incomplete outcome data

We assessed one study as low risk of attrition bias because the number of participants with missing outcome data were balanced across the intervention groups (Rebulla 1997). We assessed the two remaining studies as unclear risk of selection bias due to the lack of information on the number of participants lost to follow-up (Diedrich 2005; Heckman 1997).

Selective reporting

We assessed all three studies as unclear risk of selection bias because as study protocols were not available, it was unclear whether any of the studies were free of selective reporting (Diedrich 2005; Heckman 1997; Rebulla 1997).

Other potential sources of bias

Protocol deviation

We assessed two of the three studies as at high risk of bias due to an imbalance in protocol deviations between the different arms of the studies (Heckman 1997; Rebulla 1997). The third study was insufficiently reported for us to make an adequate assessment (Diedrich 2005). In Heckman 1997, there was a statistically significant difference between the two arms. Fourteen out of 37 participants with a transfusion threshold of 10 x 10^9/L were affected by protocol deviations, whereas only 6 out of 41 participants with

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a transfusion threshold of 20 x 10^9/L were affected. In Rebulla 1997, the pre-transfusion platelet count was higher than indicated in the protocol in 5.4% of platelet transfusions with a transfusion threshold of 10 x 10^9/L, but only 2% of platelet transfusions with a higher transfusion trigger were transfused outside the protocol guidelines; whether this was statistically significant was not reported.

Other potential sources

Two of the three studies appeared to be free of other sources of significant bias (Diedrich 2005; Rebulla 1997). The third study was insufficiently reported for us to make an adequate assessment (Heckman 1997).

Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic platelet transfusion at threshold of 10,000 compared to higher transfusion threshold (20,000 or 30,000) for people with a haematological disorder

See Summary of findings for the main comparison.

In all the included studies, the study's own definition of clinically significant bleeding was used, unless otherwise stated (Table 2). The three studies used different grading systems for assessing bleeding.

Number and severity of bleeding episodes

All three studies reported bleeding outcomes. The median study duration was less than 30 days in two studies, Heckman 1997 and Rebulla 1997, and a maximum of 37 days of observation in the third study (Diedrich 2005) (Table 1). We therefore assumed data from all three studies was relevant to the bleeding outcomes.

Number of participants with at least one bleeding episode during the first 30 days of the study

Two of the three studies reported this (Diedrich 2005; Rebulla 1997), and the author supplied data from the third study (Heckman 1997). A meta-analysis including 499 participants showed no difference between standard versus higher transfusion trigger levels (risk ratio (RR) 1.35, 95% confidence interval (CI) 0.95 to 1.90) (Analysis 1.1), nor was any difference seen if the studies comparing a threshold of 10 x 10^9/L versus 20 x 10^9/L were analysed separately (RR 1.41; 95% CI 0.95 to 2.1) (Heckman 1997; Rebulla 1997), to the study comparing a threshold of 10 x 10^9/L versus 30 x 10^9/L (RR 1.19, 95% CI 0.59 to 2.37) (Diedrich 2005).

The total number of days on which bleeding occurred during the first 30 days of the study

This outcome could have a unit of analysis problem due to participants having more than one day of bleeding. The authors of one study performed an analysis that took into account the unit of analysis issues for this outcome (Rebulla 1997). They found that the overall proportion of person-days of observation during which participants experienced WHO Grade 2 bleeding or worse was 123 out of 4005 (3.1%) and 60 out of 3330 (1.8%) for the standard and higher transfusion trigger arms, respectively, giving a relative proportion of days with WHO Grade 2 or worse bleeding (RR 1.71, 95% CI 0.84 to 3.48). A permutation test for the comparison of these proportions gives a P value of 0.162, and therefore the study authors found no significant difference between study arms. The other two studies did not take into account this unit of analysis issue (Diedrich 2005; Heckman 1997).

Number of participants with at least one episode of severe or life-threatening haemorrhage during the first 30 days of the study

Two of the studies reported the number of participants with WHO Grade 3 and 4 bleeding (Diedrich 2005; Rebulla 1997). A meta-analysis of this data showed no difference between a standard versus a higher trigger level (421 participants; RR 0.99, 95% CI 0.52 to 1.88) (Analysis 1.2).

None of the studies reported the number of participants with WHO Grade 4 bleeding alone during the first 30 days of the study. Only Diedrich 2005 reported the number of participants with bleeding that required a red cell transfusion. The study reported no significant difference between a standard versus a higher transfusion trigger level (RR 0.66, 95% CI 0.16 to 2.68) (Analysis 1.3). None of the studies reported the number of participants with bleeding that caused cardiovascular compromise.

Time to first bleeding episode from the start of study

One study reported the time to the first bleeding episode (Rebulla 1997), showing no difference between the standard and higher transfusion trigger levels (hazard ratio 1.11, 95% CI 0.64 to 1.91) (Analysis 1.4).

Mortality

All-cause mortality within 30 and 90 days

Two of the three studies reported all-cause mortality (Heckman 1997; Rebulla 1997). However, only one study reported it within a 30- or 90-day study period (Rebulla 1997) (Analysis 1.5), and

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showed no difference between a standard versus a higher transfusion trigger (RR 1.78, 95% CI 0.83 to 3.81) (Analysis 1.5).

Mortality secondary to bleeding within 30 and 90 days

All three studies reported death due to bleeding, but it was only in the largest study that any deaths occurred (Rebulla 1997). One death due to intracerebral haemorrhage in the standard trigger arm was included in the analysis (RR 2.67, 95% CI 0.11 to 64.91) (Analysis 1.6). However, two further deaths due to intracerebral haemorrhage (one in each arm of the study) occurred in participants who were randomised but not included in the analysis. If analysis of the data included all randomised participants, then there was still no evidence of a statistically significant difference in death rate between the two arms of the study (RR 1.85, 95% CI 0.17 to 20.59) (assuming that those participants for which no data forms were returned did not die secondary to bleeding) (Analysis 1.7).

Mortality secondary to infection within 30 and 90 days

One of the studies reported death due to infection (Rebulla 1997), showing no significant difference in mortality due to infection between a standard versus a higher transfusion trigger (RR 1.57, 95% CI 0.60 to 4.14) (Analysis 1.8).

Number of platelet transfusions per participant and number of platelet components per participant within 30 days from the start of the study

All three studies reported on the number of platelet transfusions required per participant (Table 3). Diedrich 2005 reported the results as medians and ranges. A meta-analysis of the other two studies, Heckman 1997 (unpublished data) and Rebulla 1997, showed a reduction in the mean number of platelet transfusions required in the standard threshold arm (mean difference (MD) (fixed effect) -2.09, 95% CI -3.20 to -0.99) (Analysis 1.9).

None of the studies reported on the number of platelet components per participant.

Number of red cell transfusions per participant and number of red cell components per participant within 30 days from the start of the study

All three studies reported on the number of red cell transfusions required (Table 4). One of the studies reported the results as medians and ranges and showed no difference in the number of red cell transfusions required. A meta-analysis of the other two studies, Heckman 1997 (unpublished data) and Rebulla 1997, showed no difference between the two arms in the mean number of red cell transfusions required (MD (fixed effect) 0.66, 95% CI -0.43 to 1.76) (Analysis 1.10).

Platelet transfusion interval within 30 days from the start of the study

None of the studies reported on the platelet transfusion interval.

Proportion of participants requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate)

None of the studies reported on additional interventions to stop bleeding.

Overall survival within 30, 90, and 180 days from the start of the study

All three studies reported all-cause survival. Only one of these studies reported overall survival within 30, 90 or 180 days, and reported actuarial survival up to 49 days after admission (Rebulla 1997). This was not significantly different between the two groups (P = 0.31).

Proportion of participants achieving complete remission within 30 days and 90 days from the start of the study

Two of the studies reported the number of participants who had achieved a complete remission (Heckman 1997; Rebulla 1997). A meta-analysis of this data showed no evidence of a difference between the two arms (333 participants; RR 0.92, 95% CI 0.78 to 1.09) (Analysis 1.11).

Total time in hospital within 30 days from the start of the study

All of the studies reported the length of time that participants were in hospital. As these were all reported as medians with ranges or interquartile ranges (Table 5), we could not perform a meta-analysis. Two of the studies reported no statistically significant difference in hospital stay between the arms of the study (Diedrich 2005; Heckman 1997), whereas the third study did not report any P values (Rebulla 1997).

Adverse effects of treatments within 30 days from the start of the study

All of the studies reported at least one adverse event of platelet transfusions.

Transfusion reactions

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Only Heckman 1997 reported on transfusion reactions secondary to platelet transfusions, and there was insufficient evidence to determine if there was a difference in the number of transfusion reactions between the two arms of the study (RR 0.07, 95% CI 0.00 to 1.09) (Analysis 1.12).

Thromboembolic disease

Only Rebulla 1997 reported deaths due to thromboembolic disease. There was one death in each arm of the study (Analysis 1.13).

Transfusion-transmitted infection

None of the studies reported on transfusion-transmitted infection.

Development of platelet antibodies

Only Diedrich 2005 reported on the development of human leukocyte antigen (HLA) antibodies. There was no difference shown between the two arms of the study (RR 1.10, 95% CI 0.07 to 17.31) (Analysis 1.14).

Development of platelet refractoriness

Two of the studies reported on the development of platelet refractoriness (Diedrich 2005; Heckman 1997). A meta-analysis involving 244 participants showed no difference between the different transfusion trigger levels (RR 0.66, 95% CI 0.16 to 2.67) (Analysis 1.15).

Quality of life (as defined by the individual studies)

None of the studies reported quality of life.

Prespecified subgroup analyses

Presence of fever

Two of the studies commented on an association between fever and bleeding risk (Heckman 1997; Rebulla 1997). However, neither of these studies reported bleeding per treatment arm for participants with or without fever.

Underlying disease

One study commented on status of underlying disease and bleeding risk (Heckman 1997).

The number of participants with at least one clinically significant bleeding episode

In Heckman 1997, the authors performed a multivariate analysis that included age (< 60 years versus ≥ 60 years), disease status (newly diagnosed versus relapsed leukaemia), and arm of the study, and there was no significant difference in the proportion of participants who bled between the standard and higher transfusion trigger levels.

Type of treatment

None of the studies reported this because in each study only one type of treatment was given (chemotherapy or allogenic stem cell transplant).

Age of participant

One study commented on age of participant and bleeding risk (Heckman 1997).

The number of participants with at least one clinically significant bleeding episode

In Heckman 1997, the authors performed a multivariate analysis that included age (< 60 years versus ≥ 60 years), disease status (newly diagnosed versus relapsed leukaemia), and arm of the study, and there was no significant difference in the proportion of participants who bled between the standard and higher transfusion trigger levels.

Platelet component dose

Two of the three included studies used a platelet component dose similar to the intermediate dose used by Slichter 2010 ($2.2 \times 10^{11}/m^2 \pm 25\%$) (Diedrich 2005; Heckman 1997), and one study used a dose between the intermediate and low dose used by Slichter 2010 ($1.1 \times 10^{11}/m^2 \pm 25\%$) (Rebulla 1997). Assuming a body surface area of 1.79 m^2 (Sacco 2010), an intermediate platelet component dose equates to $3.9 \times 10^{11} \pm 1.0 \times 10^{11}$, and a low platelet component dose equates to $2.0 \times 10^{11} \pm 0.5 \times 10^{11}$. Only one analysis that included more than one study was affected by removing the data from (Rebulla 1997); this was the number of participants with a significant bleeding event. If only the two higher-dose studies were included in the analysis, there was a difference between the standard and higher transfusion triggers (RR 1.71, 95% CI 1.04 to 2.82) (Analysis 1.16). However, there was no evidence of a difference between the two platelet component dose subgroups in this analysis (test for subgroup differences: $Chi^2 = 1.73$, df = 1 (P = 0.19), $I^2 = 42.1\%$), and therefore only the overall result that showed no evidence of a difference should be considered.

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DISCUSSION

Summary of main results

This Cochrane systematic review intended to answer the question, which threshold should be used to trigger the transfusion of prophylactic platelets in participants with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation ? Only one of the four planned comparisons could be performed. No studies compared:

- a lower platelet count threshold (5 x 10^9/L) versus a standard platelet transfusion threshold (10 x 10^9/L);
- different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L);
- alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number).

Three RCTs met our inclusion criteria for this review, all of which had data available and compared a standard platelet transfusion threshold (10 x 10^9/L) versus a higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L).
These trials were carried out from 1991 to 2001 and enrolled 520 participants from fairly comparable patient populations.
The findings of the review led to the following main conclusions:
Overall, a standard transfusion trigger of 10 x 10^9/L appears to be as effective as a higher transfusion trigger of 20 x 10^9/L or 30 x 10^9/L at preventing clinically significant bleeding. This included no evidence of a difference in the:

- number of participants with a clinically significant bleeding event (WHO Grade 2 or above);
- number of days with clinically significant bleeding (adjusted for repeated events);
- number of participants with severe or life-threatening bleeding;
- time to first clinically significant bleeding episode.

This effect was seen irrespective of the participant's age or underlying disease stage. However, all of this evidence was of low quality, due to risk of bias within the included studies and imprecision of the estimate due to the small total numbers of participants, events, or both.

- There was a reduction observed in the number of platelet transfusions required using a threshold of 10 x 10^9/L.
- There was no evidence of a difference in all-cause mortality.
- None of the studies reported quality of life.

There were no differences between the groups with regards to mortality due to bleeding or infection, red cell transfusion requirements, survival, remission rates, hospital stay, or adverse events.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of a a standard platelet transfusion threshold (10 x 10^9/L) versus a higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) to guide administration of prophylactic platelet transfusions.
The effectiveness and safety of the three other planned comparisons could not be evaluated because no study assessed these comparisons. These planned comparisons were:

- a lower platelet count threshold (5 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L);
- different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L);
- alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number).

(See How the intervention might work for further information on why these planned comparisons were clinically relevant.)
This updated review identified no new studies and no ongoing studies. It is unclear why no future studies are planned; it may be because of the large number of participants required within a study to demonstrate a statistically significant difference (Zisk 2014).
There was no evidence that people with haematological disorders receiving myelosuppressive chemotherapy or HSCT had an increase in clinically significant bleeding events with a standard platelet count threshold compared to a higher platelet count threshold.
The results of this meta-analysis should not be interpreted without considering the impact of the following factors:

- The recording of bleeding is subjective, and all three included studies used different grading systems to measure the severity of bleeding (Table 2).
- No difference was demonstrated in the number of participants with clinically significant bleeding, but the 95% confidence interval (0.95 to 1.9) demonstrates that a clinically important difference in the proportion of participants with bleeding could have been missed. When combined, the studies were not adequately powered to detect a difference. In Rebulla 1997, which included 255 participants, the power calculations were based on the assumption that the rate of WHO Grade 2 or above bleeding was 30%, but the actual rate in this study was 20%. If we assume the rate of bleeding was similar in all three studies, to detect a 50% increase in the rate of bleeding (i.e. from 20% to 30%) with 80% power would require 293 participants per arm of the study (586 in total), and to detect a 25% increase in the rate of bleeding (i.e. from 20% to 25%) with 80% power would require 1098 participants per arm of the study (2196 in total). As there were only 499 participants within all three studies, the meta-analysis would not be sufficiently powered to

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detect a 50% increase in the rate of bleeding in the restrictive transfusion arm.

- There were important differences between the studies that might affect the degree of confidence that can be placed on the assertion of equivalence between higher (20 or 30 x 10^9/L) and standard (10 x 10^9/L) platelet count thresholds for prophylactic platelet transfusions. The treatment protocols for administration of platelets varied, particularly the circumstances for which platelet transfusions could be given. In Rebulla 1997, platelets could be given to participants in the 10 x 10^9/L threshold arm if the platelet count was in the range of 10 to 20 x 10^9/L and the participant's temperature was above 38°C. This meant that 22.6% of platelet transfusions were given above the threshold of 10 x 10^9/L. In Diedrich 2005 and Heckman 1997, there were no changes in the transfusion threshold in the presence of fever.
- Not all endpoints from all the studies could be incorporated into a meta-analysis due to differences in the ways the studies had reported the outcomes.
- Some of the planned outcomes were not reported by any of the studies.
- In all studies, the number of participants that were lost to follow-up was quite low, and therefore there were minimal implications of missing data outcomes.

Quality of the evidence

All studies were RCTs, however they were all prone to bias and had threats to validity. The ability to assess the risk of bias was limited by most of the studies not reporting study methodology in adequate detail. For example, only one of the three studies reported allocation concealment as adequate (Rebulla 1997), and in all three studies blinding of participants was unknown.
None of the studies blinded medical staff caring for the participants to their patient's study allocation, and two of the three studies did not blind outcome assessors to the participants' study allocations (Heckman 1997; Rebulla 1997). This is likely to reflect the inherent difficulties with blinding platelet transfusion trials because medical staff caring for participants cannot be blinded to their patients' blood results.
We assessed the GRADE quality of evidence as low for:

- number of participants with at least one clinically significant bleeding event up to 30 days from study entry;
- number of participants with WHO Grade 3 or 4 bleeding up to 30 days from study entry;
- time to first clinically significant bleeding event;
- mortality from all causes up to 30 days from study entry;
- number of platelet transfusions per participant.

The quality of the evidence was low due to risk of bias within the included studies and imprecision of the estimate due to the small total numbers of participants, events, or both.

We did not perform a GRADE assessment of quality of the evidence for quality of life because no study reported this outcome, or for number of days with bleeding, as we relied on the study authors' own analysis.

Potential biases in the review process

There were no obvious biases within the review process. We conducted a wide search, which included ongoing trial databases and contact with researchers in the field; we carefully assessed the relevance of each paper identified; and we made no restrictions for the language in which the paper was originally published or its publication status. We performed all screening and data extractions in duplicate. We prespecified all outcomes and subgroups prior to analysis. The numbers of included studies were insufficient for us to combine to complete a funnel plot in order to examine the risk of publication bias.

Agreements and disagreements with other studies or reviews

One platelet transfusion review was recently published in this area (Kumar 2014). Kumar 2014 performed a systematic review of the use of platelet transfusions in common clinical settings, including the comparison of prophylactic versus therapeutic platelet transfusions. Their review identified the same three studies included in this review (Diedrich 2005; Heckman 1997; Rebulla 1997), as well as including the data from Zumberg 2002. We excluded the data from Zumberg 2002 from this review because fewer than 80% of participants had a haematological malignancy, and no subgroup data were available. The Zumberg 2002 study was at high risk of bias due to the significant number of platelet transfusions (31.9%) given above the level of 10 x 10^9/L.
The Kumar 2014 review only included the outcome measures of all-cause mortality, mortality due to bleeding, bleeding ("major" or "significant" bleeding as defined in each study), and number of platelet transfusions. They found no difference in significant bleeding between a standard and higher threshold and a significant decrease in the number of platelet transfusions. This was similar to the finding of our review.
The Kumar 2014 review did not perform a detailed assessment of the risk of bias of the included studies, nor did it consider reasons for heterogeneity between the included studies. Our review is more comprehensive and includes data on different bleeding outcome measures, adverse effects of transfusion, and unpublished study data provided by the authors. We have performed a detailed quality assessment of all identified studies and highlighted their weaknesses and shortcomings.

AUTHORS' CONCLUSIONS

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Implications for practice

The evidence from this review does not clearly show equivalence of a threshold of 10 x 10^9/L and 20 x 10^9/L or 30 x 10^9/L due to the imprecision of the estimates for the outcomes measured within this review (number of participants with at least one clinically significant bleeding event up to 30 days from study entry; number of participants with WHO Grade 3 or 4 bleeding up to 30 days from study entry; time to first clinically significant bleeding event; mortality from all causes up to 30 days from study entry; number of platelet transfusions per participant). However, without further evidence it is reasonable to continue with the current practice of a platelet transfusion threshold of 10 x 10^9/L in the absence of other risk factors for bleeding. This practice reduces platelet utilisation and donor exposure.

The effectiveness and safety of the three other planned comparisons cannot be commented on because no study assessed these comparisons. These planned comparisons were: a lower platelet count threshold (5 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L); different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L); alternative thresholds to guide prophylactic platelet transfusions (for example platelet mass, immature platelet fraction, absolute immature platelet number).

Implications for research

Conclusions on the non-inferiority of a platelet count threshold of 10 x 10^9/L compared to 20 x 10^9/L or 30 x 10^9/L have been based on underpowered studies leading to imprecise estimates for the outcomes within this review. In the Rebulla 1997 study (255 participants), the power calculations were based on the assumption that the rate of WHO Grade 2 or above bleeding was 30%, but the actual rate in this study was 20%. To detect a 50% increase in the rate of bleeding (that is from 20% to 30%) with 90% power would require 392 participants per arm of the study, and to detect a 25% increase in the rate of bleeding (that is from 20% to 25%) with 80% power would require 1098 participants per arm of the study. The combined results from all three studies would not be sufficiently powered to detect a 50% increase in the rate of bleeding in the standard platelet transfusion threshold (10 x 10^9/L) arm, if we assumed the rate of bleeding was 20% in all three studies.

No RCTs have compared a lower platelet count threshold (5 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L); different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L); or alternative thresholds to guide prophylactic platelet transfusions (for example platelet mass, immature platelet fraction, absolute immature platelet number) in people with haematological malignancies.

Additional evidence is required from new RCTs to determine the most appropriate platelet transfusion threshold to guide prophylactic platelet transfusions.

Assessment of bleeding in future trials

One of the difficulties within this review was the variability between studies in assessing and grading bleeding. The WHO classification of bleeding, although widely used, has never been validated, and therefore the assumption that all Grade 2 bleeding is clinically significant has been brought into question. For future studies, an international consensus on assessing and grading bleeding would greatly enhance the ability to compare platelet transfusion trials. This would need to be validated and to take into account the impact that bleeding has upon the patient from both a medical perspective and with regard to quality of life.
It is acknowledged that blinding in platelet transfusion trials is difficult. However, whenever possible, the bleeding assessor should be blinded to the intervention.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Diedrich 2005

Methods	Parallel RCT (enrolled September 1996 to September 2001). Single centre. Sweden
Participants	**Inclusion criteria:** People undergoing an allogeneic haematopoietic stem cell transplant. All ages **Exclusion criteria:** People with a known bleeding disorder or coagulopathy N = 166 (all included in analysis) **Arm 1** N = 79 (acute leukaemia N = 47; chronic leukaemia N = 20; non-malignant haematological disorder N = 4; other malignancy N = 8) **Arm 2** N = 87 (acute leukaemia N = 36; chronic leukaemia N = 24; non-malignant haematological disorder N = 11; other malignancy N = 16)
Interventions	Comparison between prophylactic platelets with different transfusion triggers **Arm 1** (Low transfusion trigger): If platelet count < 10 x 10^9/L **Arm 2** (High transfusion trigger): If platelet count < 30 x 10^9/L In both arms prior to an operation or a biopsy, a platelet count > 50 x 10^9/L was aimed for. **Platelet dose** (mean ± SD): • (buffy coat) approximately 410 x 10^9 ± 20 x 10^9 • (apheresis) approximately 380 x 10^9± 20 x 10^9 **Platelet type:** pooled random-donor platelets (buffy coat) 85% of platelet transfusions given; apheresis 15% of platelet transfusions given. All were ABO matched, irradiated, and leucodepleted
Outcomes	**Primary outcome:** Number of platelet transfusions **Secondary outcomes:** • RBC transfusions • Haemorrhages • GvHD • Transplantation-related mortality • Survival **Average number of days participants on study** Not reported
Bleeding scale	WHO **Grade 1:** petechiae **Grade 2:** mild blood loss **Grade 3 - 4:** gross or debilitating blood loss **Definition of significant bleeding:** WHO Grade 2 - 4 **Definition of life-threatening bleeding:** Not stated
Bleeding assessment	Daily bleeding assessment by nursing staff if inpatient, twice weekly bleeding assessment by nursing staff if outpatient
Red cell transfusion policy	RBCs were transfused when haemoglobin decreased below 80 g/L

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Notes	**Participants randomised:** documentation for study started 7 days prior to transplant **Follow-up:** until 30 days post-stem cell transplant **Stopping rules:** not reported **Source(s) of funding:** Supported by grants from: The Swedish Cancer Society (0070-B99-13XAC); The Children's Cancer Foundation (2000/067, 02/074); The Swedish Medical Research Council (K2000-06X-05971-20A); The Swedish Foundation for Medical Research; The Swedish Society of Medicine (2000-02-0553, 2001-1299); The Cancer Society in Stockholm; The Tobias Foundation **Conflicts-of-interest statement:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised after stratification, method of randomisation not stated
Allocation concealment (selection bias)	Unclear risk	Participants were randomised after stratification, method of allocation concealment not stated
Blinding of participants and personnel (performance bias) Participant	Unclear risk	It was unclear whether participants were blinded to the intervention, this was not reported in the published study
Blinding of participants and personnel (performance bias) Physician/Medical Staff	High risk	All platelet units were ordered by a nurse in charge of and responsible for the participant. The nurse was not blinded to the treatment arm for practical reasons
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses from the ward, blinded to treatment arm, performed daily (inpatients) or twice weekly (outpatients) assessment and reported this. All platelet units were ordered by a different nurse in charge of and responsible for the participant. He or she was not blinded to the treatment arm for practical reasons. A special research nurse collected all data for the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to make an assessment
Selective reporting (reporting bias)	Unclear risk	No protocol available to assess whether all prespecified outcomes have been reported
Other bias	Low risk	The study appears to be free of other sources of bias

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Diedrich 2005 (*Continued*)

Protocol Deviation balanced?	Unclear risk	In participants with WHO Grade 2 - 4 bleeding, violations of the protocol occurred in 4/14 participants in Arm 1 and 3/13 participants in Arm 2. The number of transfusions in which a protocol deviation occurred was not reported. Whether there were any protocol deviations in those participants that did not bleed was not reported

Heckman 1997

Methods	Parallel RCT (enrolled April 1991 to November 1995). Single centre. United States
Participants	**Inclusion criteria:** Unequivocal diagnosis of acute leukaemia (AML, ALL in relapse, acute undifferentiated leukaemia or MDS transformed to AML). Age > 17 years. Person undergoing initial induction chemotherapy or re-induction following relapse **Exclusion criteria:** APL. Inherited clotting disorder. Uncontrolled infection at randomisation. History of a bleeding diathesis. DIC at randomisation into the study. Prior entry into the study. Concomitant malignancy or AIDS diagnosis. History of platelet refractory status N = 82 entered into study; 4 ineligible (2 delayed cytogenetic diagnosis of APL. 2 not assessable, transferred to ITU within 24 hrs of registration with severe infections) **Arm 1:** N = 37 **Arm 2:** N = 41
Interventions	Comparison between prophylactic platelets with different transfusion triggers **Arm 1** (Low transfusion trigger). If platelet count $\leq$ 10 x 10^9/L **Arm 2** (High transfusion trigger). If platelet count $\leq$ 20 x 10^9/L Platelets given in both arms if serious or life-threatening bleeding and for procedures at discretion of physician ***Platelet dose:*** 1 apheresis unit (approximately 4 to 4.9 x 10^{11} of platelets) ***Platelet type:*** apheresis. Leucodepleted
Outcomes	Main or primary outcome not stated Outcomes mentioned: • Survival (at time of analysis) • Remission rates (time period not stated) • Bleeding episodes per participant • Transfusion requirements (platelets, red cells) • Hospital stay • Adverse events **Number of days participants on study (median):** Arm 1: 24 days Arm 2: 24 days

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Heckman 1997 (*Continued*)

Bleeding scale	Severity was graded using a standardised toxicity scale (Ajani 1990) **Grade 1:** petechiae, minimum blood loss, blood transfusion not required **Grade 2:** blood loss requiring transfusion of 1 to 2 units of blood **Grade 3:** blood loss requiring transfusion of 3 to 4 units of blood **Grade 4:** blood loss requiring transfusion of > 4 units of blood **Definition of significant bleeding:** requirement for therapeutic platelet transfusion (unpublished) **Definition of life-threatening bleeding:** not stated
Bleeding assessment	Bleeding episodes defined as blood loss documented in physician or nursing notes or observed by an investigator
Red cell transfusion policy	Not stated
Notes	**Participants randomised:** no definition **Follow-up of participants:** until unsupported platelet count > 30 x 10^9/L for 2 days OR transfer to intensive care for > 2 days OR discharge from hospital OR death **Stopping guideline:** not reported **Source(s) of funding:** Iowa Leukemia and Cancer Research Fund; The Dr. Richard O. Emmons Memorial Fund; L. McGilliard-T. Johannes Memorial Fund; The Mamie C. Hopkins Fund **Conflicts-of-interest statement:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation "by selecting randomised cards from envelopes". No comment on how cards were randomised Randomisation stratified by 4 groups (new diagnosis < 60 years; new diagnosis = 60 years; relapse < 60 years; relapse = 60 years)
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not described. It was not mentioned whether envelopes were opaque or sealed
Blinding of participants and personnel (performance bias) Participant	Unclear risk	It was unclear whether participants were blinded to the intervention, this was not reported in the published study
Blinding of participants and personnel (performance bias) Physician/Medical Staff	High risk	Bleeding assessors were not blinded to the intervention (additional data supplied by the author and reported in Estcourt 2013) . Bleeding assessors included medical staff (nurses and physicians routinely involved with patient care)

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Heckman 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Bleeding assessors were not blinded to the intervention (additional data supplied by the author and reported in Estcourt 2013) . Bleeding assessors were a mixture of medical staff (nurses and physicians routinely involved with patient care) and trained research nurses/research investigators
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment
Selective reporting (reporting bias)	Unclear risk	No study protocol available, and outcomes not clearly stated
Other bias	Unclear risk	Insufficient information to assess
Protocol Deviation balanced?	High risk	In Arm 1 30/311 transfusions deviated from the protocol, whereas in Arm 2 only 7/457 transfusions deviated from the protocol. This affected 14/37 participants in Arm 1 and 6/41 participants in Arm 2 (P = 0.02)

Rebulla 1997

Methods	Parallel RCT (enrolled from March 1994 to March 1996). Multicentre study (21 centres) . Italy
Participants	**Inclusion criteria:** People with AML; adolescents and adults (aged 16 to 70 yrs); admitted to hospital for 1st course of induction chemotherapy **Exclusion criteria:** People diagnosed with promyelocytic leukaemia or secondary AML; people who had received a blood transfusion prior to diagnosis of AML N = 329 people screened for trial. 276 randomised. (37 secondary leukaemia; 10 blood transfusion prior to diagnosis; 4 did not meet age criteria; 2 declined to give consent) **Arm 1:** N = 144; 9 not included in analysis: 8 alive at discharge (no study records received); 1 death on day 5 (cerebral haemorrhage) (no study records received) **Arm 2**: N = 132; 12 not included in analysis: 8 alive at discharge (no study records received); 2 died within 24 hours of admission (1 cerebral haemorrhage, 1 cardiac arrest) ; 2 received non-myeloablative course of chemotherapy
Interventions	Comparison between prophylactic platelets with different transfusion triggers **Arm 1:** (Low transfusion trigger). If platelet count < 10 x 10^9/L AND temperature < 38°C If platelet count 10 to 20 x 10^9/L AND temperature > 38°C OR in presence of major or minor bleeding OR if invasive procedures were necessary **Arm 2:** (High transfusion trigger). If platelet count < 20 x 10^9/L **Platelet dose:** 1 unit of platelet rich plasma or buffy coat concentrate per 10 kg body weight or 1 apheresis concentrate given. Number of platelets per transfusion (apheresis)

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	median 280 x 10^9 (range 110 to 588), pooled concentrate median 217 x 10^9 (range 140 to 555) **Platelet type:** Apheresis platelets given to 50% of participants in Arm 1 and 42% of participants in Arm 2
Outcomes	**Primary outcome:** Frequency and severity of haemorrhage **Secondary outcomes:** • Mortality rates • Rates of complete remission • Number of red cell transfusions • Number of platelet transfusions All outcomes measured to end of study **Number of days participants on study (mean)** Arm 1 = 29.7 days Arm 2 = 27.8 days
Bleeding scale	Severity of haemorrhage marked on an 8-point scale **0** = no bleeding **1** = petechiae or mucosal or retinal bleeding **2** = melaena, haematemesis, haematuria, or haemoptysis **3** = any bleeding requiring a red cell transfusion **4** = retinal bleeding accompanied by visual impairment **5** = non-fatal cerebral bleeding **6** = fatal cerebral bleeding **7** = fatal non-cerebral bleeding **Definition of significant haemorrhage:** score > 1 **Definition of life-threatening haemorrhage:** not stated
Bleeding assessment	The physician in charge of the participant collected data on the occurrence and type of bleeding
Red cell transfusion policy	Red cells were given when haemoglobin < 80 g/L
Notes	**Participants randomised at:** diagnosis **Follow-up of participants:** until platelet count > 100 x 10^9/L OR discharge from hospital OR occurrence of complete remission OR resistance to chemotherapy OR death **Stopping guidelines:** The trial was scheduled to be stopped if the rate of outcome events reached statistical significance (P < 0.01 by the Chi^2 test) Acetaminophen was used as an antipyretic agent **Source(s) of funding:** not reported **Conflicts-of-interest statement:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants underwent randomisation as soon as the diagnosis and other inclusion criteria were communicated by telephone

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		to the central randomisation centre at the GIMEMA secretariat in Rome. A random permutated block design was used in the individual centres
Allocation concealment (selection bias)	Low risk	The people who handled randomisation, data management, and statistical analysis were not involved in the treatment of the participants
Blinding of participants and personnel (performance bias) Participant	Unclear risk	It was unclear whether participants were blinded to the intervention, this was not reported in the published study
Blinding of participants and personnel (performance bias) Physician/Medical Staff	High risk	Medical staff routinely involved in the care of the participant were the bleeding assessors and were not blinded to the intervention (additional data supplied by the author and reported in Estcourt 2013)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Bleeding assessors were not blinded to the intervention (additional data supplied by the author and reported in Estcourt 2013)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. 21 of the randomised participants were excluded from analysis (16 no study records received. 2 received non-myeloablative chemotherapy. 3 died (2 within 24 hours of enrolment into the study); 2 of the three deaths were due to an intracerebral haemorrhage. 9 participants were excluded in the standard-trigger arm: 8 alive at discharge (no study records received); 1 death on day 5 (cerebral haemorrhage) (no study records received). 12 participants were excluded in the higher-trigger arm: 8 alive at discharge (no study records received); 2 died within 24 hours of admission (1 cerebral haemorrhage, 1 cardiac arrest); 2 received non-myeloablative course of chemotherapy
Selective reporting (reporting bias)	Unclear risk	Study protocol not available to allow judgement
Other bias	Low risk	The study appears to be free of other sources of bias

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Protocol Deviation balanced?	High risk	Pre-transfusion platelet count higher than indicated in the protocol in 5.4% of platelet transfusions in Arm 1 and 2% of platelet transfusions in Arm 2

ALL = acute lymphocytic leukaemia
AML = acute myeloid leukaemia
APL = acute promyelocytic leukaemia
DIC = disseminated intravascular coagulation
GvHD = graft versus host disease
ITU = intensive treatment unit
MDS = myelodysplastic syndrome
RBC = red blood cell
RCT = randomised controlled trial
SD = standard deviation

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

Study	Reason for exclusion
Aderka 1986	A non-randomised retrospective study
Agliastro 2006	Comparison of apheresis versus buffy coat platelet transfusions (abstract)
Akkök 2007	Comparison of apheresis versus buffy coat platelet transfusions
Anderson 1997	Comparison of apheresis versus buffy coat -derived versus platelet rich plasma -derived platelet products
Andreu 2009	Review
Andrew 1993	Wrong patient group - premature infants
Arnold 2004	Comparison of apheresis versus whole blood -derived platelet transfusions
Arnold 2006	Wrong patient group - intensive treatment unit
Avvisati 2003	Review
Bai 2004	Wrong patient group - solid tumours
Benjamin 2002	Review
Bentley 2000	Comparison of autologous versus allogeneic platelet transfusions

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(*Continued*)

Blajchman 2008	Review
Blumberg 2002	Comparison of washed versus standard platelet transfusions
Blumberg 2004	Comparison of washed versus standard platelet transfusions
Blundell 1996	Comparison of standard versus pathogen inactivated platelets
Buhrkuhl 2010	Review
Callow 2002	A non-randomised prospective study with historical control
Cameron 2007	A non-randomised prospective study
Carr 1990	Comparison of ABO-matched versus mismatched platelet products
Casbard 2004	Systematic review and wrong patient group
Chaoui 2005	Observational prospective study
Chaurasia 2012	A non-randomised prospective study
Cid 2007	Systematic review of differing platelet transfusion doses
Corash 2001	Comparison of intercept platelet components versus standard platelet components
Couban 2002	Comparison of plasma reduction and leucodepletion
de Wildt-Eggen 2000	Comparison of platelet concentrates in plasma versus additive solution
Decaudin 2004	Non-randomised prospective study
Di Pietro 1998	Comparison of HLA -matched versus random -donor apheresis platelet components
Diedrich 2009	Comparison of platelet products stored 1 - 5 versus 6 - 7 days
Dumont 2011	Comparison of buffy coat versus platelet rich plasma platelet concentrates
Dzik 2004	Review
Eder 2007	Non-randomised observational study
Elting 2002	Retrospective analysis - lymphoma and solid tumours
Elting 2003	Non-randomised retrospective cohort - lymphoma and solid tumours
Fanning 1995	Wrong patient group - gynaecological cancer

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(*Continued*)

Follea 2004	Guideline
Friedmann 2002	A non-randomised retrospective analysis
Gajic 2006	Wrong patient group - intensive treatment unit
Gerday 2009	Wrong patient group - neonates
Gil-Fernandez 1996	A non-randomised retrospective historical control study (different platelet transfusion thresholds)
Gmür 1983	Comparison of single -donor versus pooled platelet products
Gmür 1991	A non-randomised prospective cohort observational study (different platelet transfusion thresholds)
Goodnough 2001	Fewer than 80% of participants diagnosed with a haematological disorder - different platelet doses
Goodnough 2002	Review
Goodnough 2005	Review
Goodrich 2008	Comparison of pathogen inactivated versus standard apheresis platelets
Greeno 2007	A non-randomised prospective observational study (different platelet transfusion thresholds)
Grossman 1980	Comparison of prophylactic versus therapeutic platelet transfusions
Gurkan 2007	Comparison of apheresis versus pooled platelet products
Hardan 1994	A non-randomised observational study, therapeutic platelets only, historical control reported only as an abstract
Harrup 1999	Comparison of buffy coat plasma versus T-sol platelet transfusions
Heal 1993	Comparison of ABO -compatible versus mismatched platelet transfusions
Heal 2004	Review
Heddle 1994	Comparison of plasma from platelet concentrates versus platelets
Heddle 1999	Comparison of plasma removal versus leucodepletion
Heddle 2002	Comparison of plasma removal versus leucodepletion
Heddle 2003	Systematic review - methods of assessing bleeding outcome
Heddle 2005	Comparison of whole blood -derived platelets stored as a pool versus individually

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(*Continued*)

Heddle 2007	Review
Heddle 2009	Comparison of a low dose versus standard platelet component dose
Higby 1974	Comparison of prophylactic platelets versus platelet poor plasma
ISRCTN01292427	Comparison of dynamic light scattering-screened versus unscreened platelets
ISRCTN49080246	Comparison of 1 - 5 versus 6 - 7 day -old platelet transfusions
ISRCTN56366401	Comparison of different types of platelet component
Jelic 2006	Review
Johansson 2007	Wrong patient group - ruptured abdominal aortic aneurysm
Julmy 2009	Wrong patient group - ruptured abdominal aortic aneurysm
Kakaiya 1981	Comparison of apheresis versus pooled platelet concentrates
Kerkhoffs 2010	Comparison of standard platelets versus pathogen inactivated platelets versus platelets stored in PAS II media
Klumpp 1999	A randomised cross-over study. This study was included within the previous systematic review ; however, due to stricter inclusion/exclusion criteria, this study has now been excluded from the review Only laboratory outcomes were reported. 37% of participants had a non-haematological malignancy (breast cancer)
Kluter 1996	Comparison of random -donor platelet components from pooled buffy coats versus apheresis platelet components
Lapierre 2003	Comparison of standard apheresis platelet products versus a donor reduction policy
Lawrence 2001	A non-randomised retrospective historical control study (different platelet transfusion thresholds)
Leach 1991	Comparison of warmed versus standard platelet transfusions
Lee 1989	Comparison of ABO -matched versus mismatched platelet transfusions
Levi 2002	Review
Lordkipanidze 2009	Review
Lozano 2003	Review
Lozano 2010	Efficacy of older platelet transfusions
Lozano 2011	Comparison of pathogen inactivated versus conventional platelet products

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(*Continued*)

Lu 2011	Comparison of a low -dose versus standard -dose platelet component
Martel 2004	Review
McCullough 2004	Comparison of pathogen inactivated versus conventional apheresis platelets
McNicol 2003	Review
Messerschmidt 1988	Comparison of HLA -matched versus mismatched platelet transfusions
Mirasol 2010	Comparison of pathogen inactivated versus conventional platelet products
Murphy 1982	Comparison of a prophylactic versus therapeutic platelet transfusion policy
Murphy 1986	Comparison of HLA -matched and leucodepleted blood products
Navarro 1998	A non-randomised retrospective historical control observational study (different platelet transfusion thresholds)
NCT00699621	Wrong patient group - intracerebral haemorrhage
NCT01615146	Comparison of a prophylactic versus therapeutic platelet transfusion policy
Nevo 2007	A non-randomised retrospective analysis (different platelet thresholds)
Norol 1998	A non-randomised prospective comparison (3 different doses of platelets)
Norville 1994	Comparison of 2 different infusion pumps for platelet transfusions
Norville 1997	Comparison of 2 different infusion rates
Oksanen 1991	Comparison of pre- versus poststorage leucodepletion of p latelet rich plasma -derived platelet transfusions
Oksanen 1994	Comparison of leucodepleted buffy coat -derived platelet transfusions versus historical control
Paananen 2009	Non-randomised study (unclear whether prospective or retrospective)
Pamphilon 1996	Comparison of buffy coat platelet components, single -donor apheresis non-leucocyte depleted and single -donor apheresis leucocyte-depleted platelet components
Paramo 2004	Review
Poon 2003	Review
Qureshi 2007	Audit of platelet transfusions in the United Kingdom
Rabinowitz 2010	Review

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(*Continued*)

Rayment 2005	Review
Razzaghi 2012	Systematic review of platelet transfusion threshold in people with gastrointestinal bleeding
Rebulla 2009	Comparison of pathogen inactivated versus standard platelet components
Reed 1986	Wrong patient group - massive transfusion
Roberts 2003	Review
Roy 1973	Comparison of different platelet component doses
Sagmeister 1999	A non-randomised retrospective study (aplastic anaemia)
Sakakura 2003	Review
Samama 2005	Guideline
Schiffer 1983	Comparison of leucodepleted versus standard platelet concentrates
Sensebe 2004	Comparison of different platelet component doses
Shanwell 1992	Comparison of fresh versus stored platelets
Shehata 2009	Systematic review - ABO -identical versus non-identical platelet transfusions
Shen 2007	Review
Singer 1988	Single -donor HLA -matched versus random -donor platelets
Sintnicolaas 1981	Comparison of single -donor and multiple -donor platelet components
Sintnicolaas 1982	Comparison of a prophylactic versus therapeutic platelet transfusion policy
Sintnicolaas 1995	Comparison of leucocyte depleted versus standard platelets
Slichter 1998	Comparison of apheresis versus pooled platelet components
Slichter 2004	Review
Slichter 2006	Comparison of pathogen inactivated versus conventional apheresis platelets
Slichter 2007	Review
Slichter 2010	Comparison of different platelet component doses
Slichter 2012	Review

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(*Continued*)

Solomon 1978	Comparison of a prophylactic versus therapeutic platelet transfusion policy
Sosa 2003	Review
Spiess 2004	Wrong patient group - cardiac
Stanworth 2013	Comparison of a prophylactic versus therapeutic platelet transfusion policy
Steffens 2002	Comparison of different platelet component doses
Strauss 2004	Review
Strauss 2005	Review
Strindberg 1996	Comparison of apheresis versus buffy coat platelet products
Sweeney 2000	Comparison of pre-storage leucodepleted versus bedside leucodepleted platelets
Tinmouth 2003	Review
Tinmouth 2004	Comparison of low -dose platelet components versus standard -dose platelet components
Tosetto 2009	Guideline
TRAP 1997	Comparison of standard pooled platelet product versus irradiated pooled platelet product versus leucodepleted pooled platelet product versus apheresis platelet product
Vadhan-Raj 2002	Wrong patient group - gynaecological malignancy
Van Marwijk 1991	Comparison of leucodepleted platelet products prepared by filtration or centrifugation
van Rhenen 2003	Comparison of pathogen inactivated versus standard buffy coat -derived platelet transfusions
Velik-Salchner 2007	Non-human study
Verma 2008	A non-randomised observational study
Wandt 1998	A non-randomised prospective cohort study (not randomised at the participant level)
Wandt 2005	A non-randomised prospective study with an historical case control (therapeutic versus prophylactic platelet transfusions)
Wandt 2006	A non-randomised prospective study with an historical case control (therapeutic versus prophylactic platelet transfusions)
Wandt 2010	Review
Wandt 2012	Comparison of a prophylactic versus therapeutic platelet transfusion policy

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(*Continued*)

Wang 2002	A comparison of acetaminophen and diphenhydramine versus placebo as premedication for platelet transfusions
Wang 2005	Review
Weigand 2009	Prospective observational study
Williamson 1994	Comparison of standard versus bedside leucodepleted platelet products
Woodard 2002	Review
Zahur 2002	Prospective observational study
Zeller 2014	Review
Zhao 2002	Comparison of leucodepleted versus standard platelet transfusions
Zumberg 2002	This study was included within the previous systematic review ; however, due to stricter inclusion/exclusion criteria, this study has now been excluded from the review 31% of participants had a non-haematological malignancy (breast cancer)

HLA = human leukocyte antigen

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DATA AND ANALYSES

Comparison 1. Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers of participants with a significant bleeding event	3	499	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.95, 1.90]
1.1 Platelet threshold < 10 vs. < 20	2	333	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.95, 2.10]
1.2 Platelet threshold < 10 vs. < 30	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.59, 2.37]
2 Number of participants with WHO Grade 3 or 4 bleeding	2	421	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.52, 1.88]
2.1 Platelet threshold < 10 vs. < 20	1	255	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.58, 2.54]
2.2 Platelet threshold < 10 vs. < 30	1	166	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.14, 2.13]
3 Number of participants with bleeding requiring a red cell transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4 Time to first bleeding episode	1		Hazard Ratio (Fixed, 95% CI)	Subtotals only
5 All-cause mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Mortality due to bleeding	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Mortality due to bleeding (all randomised participants)	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Mortality due to infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9 Mean number of platelet transfusions per participant	2	333	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-3.20, -0.99]
10 Mean number of red cell transfusions per participant	2	333	Mean Difference (IV, Fixed, 95% CI)	0.66 [-0.43, 1.76]
11 Complete remission rates	2	333	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.09]
12 Numbers of participants with platelet transfusion reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13 Number of participants with thromboembolic disease	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14 Number of participants requiring HLA-matched platelets	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15 Number of participants with platelet refractoriness	2	244	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.16, 2.67]
16 Numbers of participants with a significant bleeding event	3	499	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.95, 1.90]
16.1 Platelet component dose (2.9×10^{11} to 4.9×10^{11})	2	244	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.04, 2.82]
16.2 Platelet component dose ($< 2.9 \times 10^{11}$)	1	255	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.66, 1.74]

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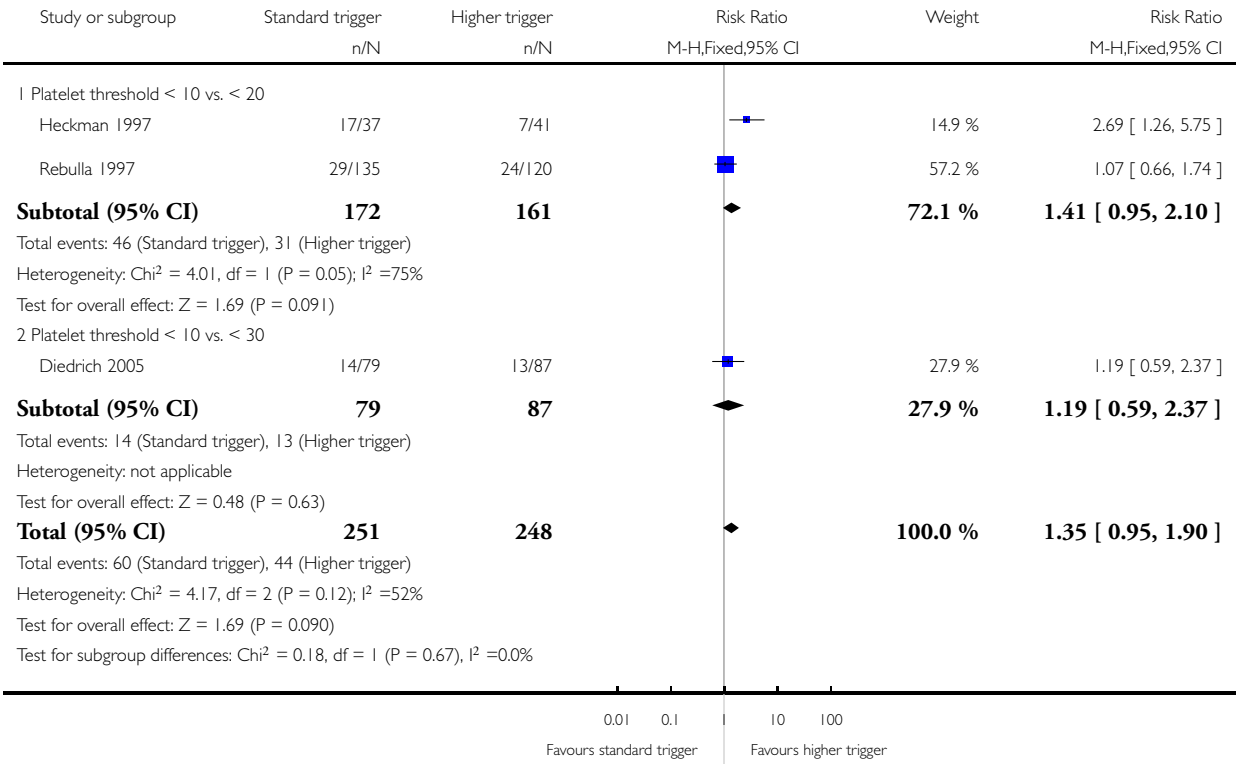
Analysis 1.1. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 1 Numbers of participants with a significant bleeding event.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 1 Numbers of participants with a significant bleeding event



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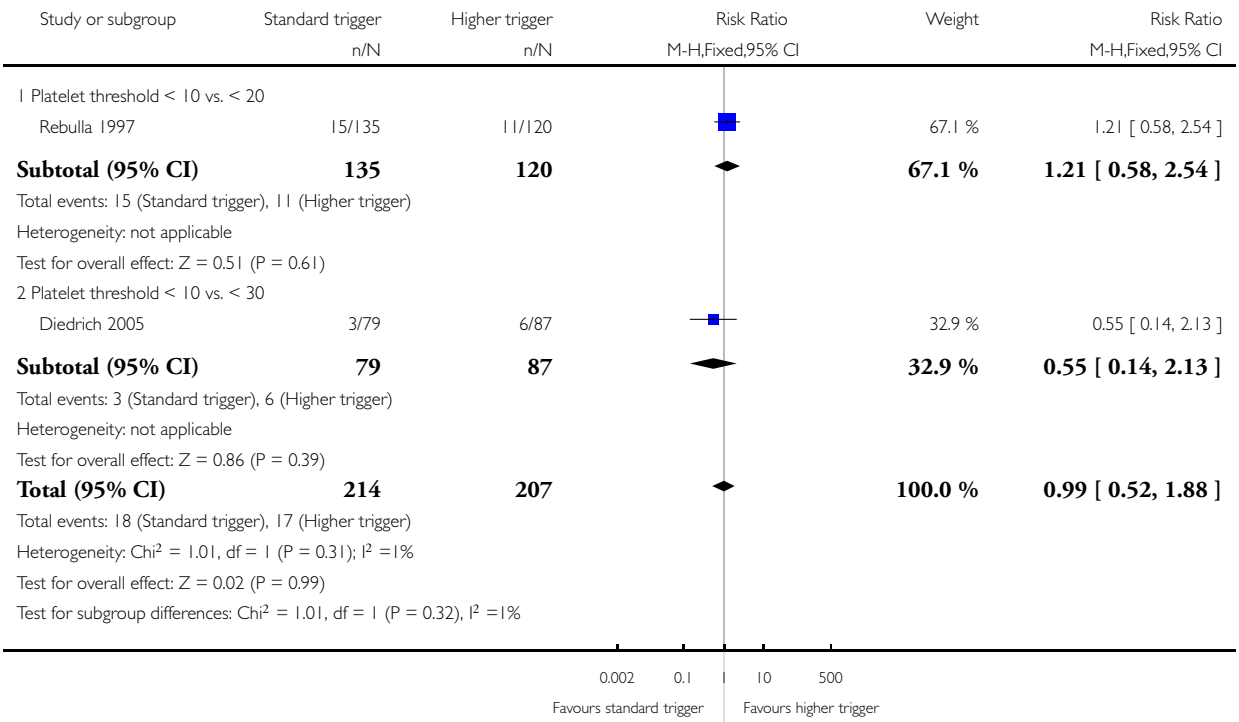
Analysis 1.2. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 2 Number of participants with WHO Grade 3 or 4 bleeding.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 2 Number of participants with WHO Grade 3 or 4 bleeding



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Analysis 1.3. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 3 Number of participants with bleeding requiring a red cell transfusion.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 3 Number of participants with bleeding requiring a red cell transfusion

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diedrich 2005	3/79	5/87			0.66 [0.16, 2.68]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 3 (Standard trigger), 5 (Higher trigger)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					



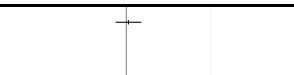
Analysis 1.4. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 4 Time to first bleeding episode.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 4 Time to first bleeding episode

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Rebulla 1997	0.1 (0.28)			1.11 [0.64, 1.91]
Subtotal (95% CI)				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



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Analysis 1.5. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 5 All-cause mortality.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 5 All-cause mortality

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rebulla 1997	18/135	9/120			1.78 [0.83, 3.81]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 18 (Standard trigger), 9 (Higher trigger)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					



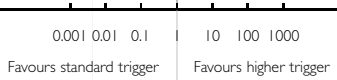
Analysis 1.6. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 6 Mortality due to bleeding.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 6 Mortality due to bleeding

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Diedrich 2005	0/79	0/87		Not estimable
Heckman 1997	0/37	0/41		Not estimable
Rebulla 1997	1/135	0/120		2.67 [0.11, 64.91]



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Analysis 1.7. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 7 Mortality due to bleeding (all randomised participants).

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 7 Mortality due to bleeding (all randomised participants)

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Diedrich 2005	0/79	0/87		Not estimable
Heckman 1997	0/37	0/41		Not estimable
Rebulla 1997	2/144	1/132		1.85 [0.17, 20.59]



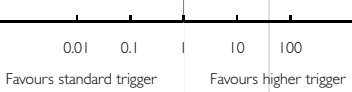
Analysis 1.8. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 8 Mortality due to infection.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 8 Mortality due to infection

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Rebulla 1997	12/135	7/120			1.57 [0.60, 4.14]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 12 (Standard trigger), 7 (Higher trigger)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					



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Analysis 1.9. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 9 Mean number of platelet transfusions per participant.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 9 Mean number of platelet transfusions per participant

Study or subgroup	Standard trigger N	Mean(SD)	Higher trigger N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heckman 1997	37	8.4 (5.3)	41	11.4 (7.1)		15.9 %	-3.00 [-5.76, -0.24]
Rebulla 1997	135	7.05 (4.56)	120	8.97 (5.17)		84.1 %	-1.92 [-3.12, -0.72]
Total (95% CI)	**172**		**161**			**100.0 %**	**-2.09 [-3.20, -0.99]**

Heterogeneity: $Chi^2 = 0.49$, df = 1 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 3.72 (P = 0.00020)

Test for subgroup differences: Not applicable



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Analysis 1.10. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 10 Mean number of red cell transfusions per participant.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

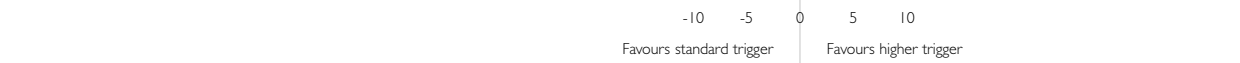
Outcome: 10 Mean number of red cell transfusions per participant

Study or subgroup	Standard trigger N	Mean(SD)	Higher trigger N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heckman 1997	37	12.2 (6.9)	41	10.7 (5.1)		16.3 %	1.50 [-1.22, 4.22]
Rebulla 1997	135	9.57 (5.18)	120	9.07 (4.58)		83.7 %	0.50 [-0.70, 1.70]
Total (95% CI)	**172**		**161**			**100.0 %**	**0.66 [-0.43, 1.76]**

Heterogeneity: Chi^2 = 0.44, df = 1 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 1.19 (P = 0.24)

Test for subgroup differences: Not applicable



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Analysis 1.11. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 11 Complete remission rates.

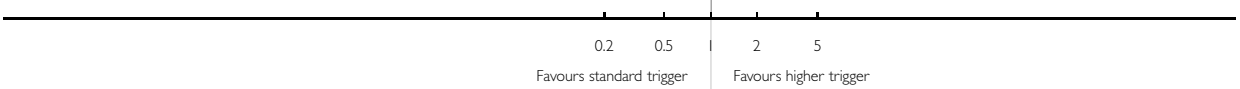
Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 11 Complete remission rates

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heckman 1997	25/37	27/41		24.1 %	1.03 [0.75, 1.40]
Rebulla 1997	76/135	76/120		75.9 %	0.89 [0.73, 1.09]
Total (95% CI)	**172**	**161**		**100.0 %**	**0.92 [0.78, 1.09]**

Total events: 101 (Standard trigger), 103 (Higher trigger)
Heterogeneity: $Chi^2 = 0.57$, df = 1 (P = 0.45); $I^2 = 0.0\%$
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 12 Numbers of participants with platelet transfusion reactions.

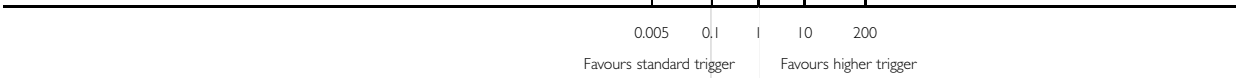
Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 12 Numbers of participants with platelet transfusion reactions

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heckman 1997	0/37	8/41			0.07 [0.00, 1.09]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**

Total events: 0 (Standard trigger), 8 (Higher trigger)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P < 0.00001)
Test for subgroup differences: Not applicable



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Analysis 1.13. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 13 Number of participants with thromboembolic disease.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 13 Number of participants with thromboembolic disease

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rebulla 1997	1/135	1/120			0.89 [0.06, 14.06]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 1 (Standard trigger), 1 (Higher trigger)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					



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Analysis 1.14. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 14 Number of participants requiring HLA-matched platelets.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 14 Number of participants requiring HLA-matched platelets

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diedrich 2005	1/79	1/87			1.10 [0.07, 17.31]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 1 (Standard trigger), 1 (Higher trigger)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 1.15. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 15 Number of participants with platelet refractoriness.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 15 Number of participants with platelet refractoriness

Study or subgroup	Standard trigger n/N	Higher trigger n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Diedrich 2005	1/79	1/87		20.1 %	1.10 [0.07, 17.31]
Heckman 1997	2/37	4/41		79.9 %	0.55 [0.11, 2.85]
Total (95% CI)	**116**	**128**		**100.0 %**	**0.66 [0.16, 2.67]**
Total events: 3 (Standard trigger), 5 (Higher trigger)					
Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					



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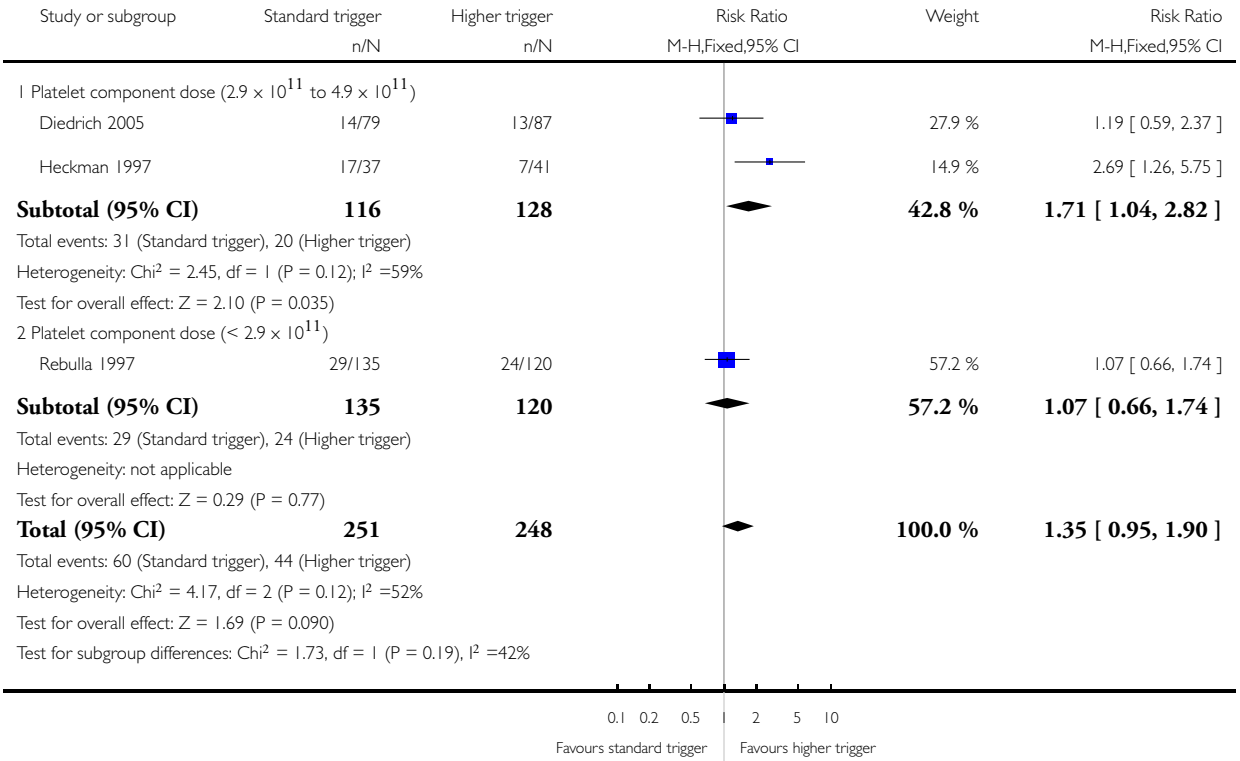
Analysis 1.16. Comparison 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level, Outcome 16 Numbers of participants with a significant bleeding event.

Review: Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Prophylactic platelet transfusion at a standard trigger level versus a higher trigger level

Outcome: 16 Numbers of participants with a significant bleeding event



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ADDITIONAL TABLES

Table 1. Characteristics of the included studies

Study	Type of participants	Number of participants	Intervention	Platelet component dose	Duration of study	Type of platelet component	Primary outcome
Diedrich 2005	All ages undergoing an allogeneic HSCT	166	Prophylactic plt transfusion if plt count < 10 x 10^9/L versus prophylactic plt transfusion if plt count < 30 x 10^9/L	Average yield (mean ± SD) 4.10 x 10^{11} ± 0.2 x 10^{11} (buffy coat) 3.80 x 10^{11} ± 0.2 x 10^{11} (apheresis)	Maximum duration of observation was 37 days (7 days pre-HSCT and 30 days post-HSCT) . No information available on the number of participants who died or were lost to follow-up	Leucodepleted, ABO-matched, irradiated pooled random-donor platelets (buffy coat) 85% Apheresis 15%	Number of platelet transfusions
Heckman 1997	Adults with acute leukaemia	82	Prophylactic plt transfusion if plt count ≤ 10 x 10^9/L versus prophylactic plt transfusion if plt count ≤ 20 x 10^9/L	1 apheresis unit. Average yield each study year (number of transfusions) 4. 9 x 10^{11} 1991 (n = 502) 4.5 x10^{11} 1992 (n = 418) 4. 7 x 10^{11} 1993 (n = 399) 4. 0 x 10^{11} 1994 (n = 400) 4. 3 x 10^{11} 1995 (n = 398)	Median 24 days	Leucodepleted Apheresis	Not reported
Rebulla 1997	Adolescents and adults with AML	276	Prophylactic plt transfusion if plt count < 10 x 10^9/L	Median 2.2 x 10^{11} (pooled) 2.8 x 10^{11}	Mean 27.8 to 29.7 days	Apheresis and pooled products	Frequency and severity of haemorrhage

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Table 1. Characteristics of the included studies (*Continued*)

			versus prophylactic plt transfusion if plt count < 20 x 10^9/L	(apheresis)			

AML = acute myeloid leukaemia
HSCT = haematopoietic stem cell transplant
plt = platelet
SD = standard deviation

Table 2. Assessment and grading of bleeding

Study	Bleeding primary outcome of study	Method of bleeding assessment reported	Bleeding severity scale used	RBC usage part of bleeding severity assessment	RBC transfusion policy
Rebulla 1997	Yes	Yes	New scale developed by Rebulla	Yes	Haemoglobin < 80 g/L
Heckman 1997	Not reported	Yes	Ajani 1990	Yes	Not reported
Diedrich 2005	No	Yes	WHO 1979	No	Haemoglobin < 80 g/L

RBC = red blood cell

Table 3. Number of platelet transfusions and number of platelet units

Study	Intervention	Number of participants in each arm	Number of platelet transfusions/ participant	Comparison statistics	P value	Number of platelet units transfused/ participant	Comparison statistics	P value
Short-term follow-up (up to 30 days)								
Diedrich 2005	**< 10 x 10^9/ L**	79	Median 4; range 0 to 32	Not reported	< 0.001	Not reported	Not reported	Not reported
	< 30 x 10^9/ L	87	Median 10; range 0 to 48			Not reported	Not reported	
Heckman 1997	**≤ 10 x 10^9/ L**	37	Mean 8.4 ± SD 5.3*	MD -3.00, 95% CI	Not reported	Not reported	Not reported	Not reported

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Table 3. Number of platelet transfusions and number of platelet units (*Continued*)

				-5.76 to -0.24*				
	≤ **20 x 10^9/L**	41	Mean 11.4 ± SD 7.1*			Not reported	Not reported	
Rebulla 1997	**< 10 x 10^9/L**	135	Mean 7.05 ± SD 4.56	MD -1.92, 95% CI -3.12 to -0.72	0.001	Not reported	Not reported	Not reported
	< 20 x 10^9/L	120	Mean 8.97 ± SD 5.17			Not reported	Not reported	

*unpublished data provided by the author. The paper provided medians and ranges median 7 (5 to 11) for the standard-trigger arm and median 11 (6 to 15) for the higher-trigger arm.
CI = confidence interval
MD = mean difference
SD = standard deviation

Table 4. Number of red cell transfusions and number of red cell units

Study	Intervention	Number of participants in each arm	Number of red cell transfusions/ participant	Comparison statistics	P value	Number of red cell units transfused/ participant	Comparison statistics	P value
Short-term follow-up (up to 30 days)								
Diedrich 2005	**< 10 x 10^9/L**	79	Median 4; range 0 to 26	Not reported	Not significant	Not reported	Not reported	Not reported
	< 30 x 10^9/L	87	Median 4; range 0 to 31			Not reported	Not reported	
Heckman 1997	≤ **10 x 10^9/L**	37	Mean 12.2 ± SD 6.9*	MD 1.50, 95% CI -1.22 to 4.22*	Not reported	Not reported	Not reported	Not reported
	≤ **20 x 10^9/L**	41	Mean 10.7 ± SD 5.1*			Not reported	Not reported	
Rebulla 1997	**< 10 x 10^9/L**	135	Mean 9.57 ± SD 5.18	MD 0.50, 95% CI -0.70 to 1.70*	Not reported	Not reported	Not reported	Not reported

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Table 4. Number of red cell transfusions and number of red cell units *(Continued)*

	< 20 x 10^9/L	120	Mean 9.07 ± SD 4.58			Not reported	Not reported	

*unpublished data provided by the author. The paper provided medians and ranges median 11 (8 to 14) for the standard-trigger arm and median 10 (6 to 14) for the higher-trigger arm (P = 0.41).
CI = confidence interval
MD = mean difference
SD = standard deviation

Table 5. Duration of hospital stay

Study	Intervention (transfusion threshold)	Number of participants in each arm	Number of days in hospital (median)	P value
Diedrich 2005	**< 10 x 10^9/L**	79	23 Range 9 to 89	Not significant
	< 30 x 10^9/L	87	23 Range 14 to 140	
Heckman 1997	**≤ 10 x 10^9/L**	37	38 IQR 30 to 42	0.25*
	≤ 20 x 10^9/L	41	32 IQR 27 to 45	
Rebulla 1997	**< 10 x 10^9/L**	135	29 Range 3 to 64	Not reported
	< 20 x 10^9/L	120	28 Range 4 to 54	

*unpublished data provided by the author.
IQR = interquartile range

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APPENDICES

Appendix 1. CENTRAL (Cochrane Library) 2015 search strategy

#1 MeSH descriptor: [Blood Platelets] explode all trees
#2 (platelet* or thrombocyte*):ti
#3 #1 or #2
#4 MeSH descriptor: [Blood Transfusion] explode all trees
#5 transfus*:ti
#6 #4 or #5
#7 #3 and #6
#8 MeSH descriptor: [Platelet Transfusion] explode all trees
#9 MeSH descriptor: [Plateletpheresis] explode all trees
#10 ((platelet* or thrombocyte*) near/5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product or products or component* or concentrate* or apheres* or pooled or single donor or random donor))
#11 thrombocytopheres* or plateletpheres*
#12 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#13 #7 or #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Hematologic Neoplasms] explode all trees
#15 MeSH descriptor: [Leukemia] explode all trees
#16 MeSH descriptor: [Lymphoma] explode all trees
#17 MeSH descriptor: [Multiple Myeloma] explode all trees
#18 MeSH descriptor: [Anemia, Aplastic] explode all trees
#19 MeSH descriptor: [Bone Marrow Diseases] explode all trees
#20 MeSH descriptor: [Thrombocytopenia] explode all trees
#21 (thrombocytope* or leukemi* or leukaemi* or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)
#22 ((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*))
#23 MeSH descriptor: [Antineoplastic Agents] explode all trees
#24 MeSH descriptor: [Stem Cell Transplantation] explode all trees
#25 MeSH descriptor: [Bone Marrow Transplantation] this term only
#26 MeSH descriptor: [Radiotherapy] explode all trees
#27 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)
#28 ((haematolog* or hematolog* or hemato-oncolog* or haemato-oncolog*) near/2 patients)
#29 (malignan* or oncolog* or cancer*):ti
#30 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 #13 and #30

Appendix 2. MEDLINE (Ovid) search strategy (Nov 2011-2015)

1. BLOOD PLATELETS/
2. (platelet* or thrombocyte*).ti.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.ti.
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. PLATELETPHERESIS/

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10. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
11. (thrombocytopheres* or plateletpheres*).tw.
12. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
13. or/7-12
14. exp Hematologic Neoplasms/
15. exp Leukemia/ or exp Lymphoma/
16. exp Multiple Myeloma/
17. exp Anemia, Aplastic/
18. exp Bone Marrow Diseases/
19. exp Thrombocytopenia/
20. (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
21. ((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.
22. exp Antineoplastic Agents/
23. exp Stem Cell Transplantation/ or Bone Marrow Transplantation/ or exp Radiotherapy/
24. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*).tw.
25. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw.
26. (malignan* or oncolog* or cancer*).ti.
27. or/14-26
28. 13 and 27

Appendix 3. PubMed search strategy (epublications only)

#1 ((platelet* OR thrombocyte*) AND (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product OR products OR component* OR concentrate* OR apheres* OR pooled OR single donor OR random donor OR protocol* OR trigger* OR threshold* OR schedul* OR dose OR doses OR dosing OR usage OR utilisation OR utilization))
#2 thrombocytopheres* OR plateletpheres*
#3 #1 OR #2
#4 (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR multiple myeloma OR plasma cell myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR Hodgkin*)
#5 ((haematolog* OR hematolog* OR blood OR red cell* OR white cell* OR lymphom* OR marrow OR platelet*) AND (malignan* OR oncolog* OR cancer OR cancers OR neoplasm*))
#6 #4 OR #5
#7 #3 AND #6
#8 (random* OR blind* OR control group* OR placebo OR controlled trial OR controlled study OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature OR medline OR cochrane OR embase) AND (publisher[sb] NOT pubstatusnihms)
#9 #7 AND #8

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Appendix 4. EMBASE (Ovid) search strategy (Nov 2011-2015)

1. Thrombocyte/
2. (platelet* or thrombocyte*).ti.
3. 1 or 2
4. Blood Transfusion/
5. transfus*.ti.
6. 4 or 5
7. 3 and 6
8. Thrombocyte Transfusion/
9. Thrombocytopheresis/
10. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
11. (thrombocytopheres* or plateletpheres*).tw.
12. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
13. or/7-12
14. Hematologic Malignancy/
15. Lymphoma/
16. NonHodgkin Lymphoma/
17. Hodgkin Disease/
18. exp Myeloproliferative Disorder/
19. exp Aplastic Anemia/
20. exp Thrombocytopenia/
21. (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
22. ((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.
23. exp Chemotherapy/
24. exp Stem Cell Transplantation/
25. exp Bone Marrow Transplantation/
26. exp Radiotherapy/
27. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant* or rituximab).tw.
28. ((haematolog* or hematolog*) adj2 patients).tw.
29. (malignan* or oncolog* or cancer*).ti.
30. or/14-29
31. 13 and 30

Appendix 5. CINAHL (EBSCOhost) search strategy (Nov 2011-2015)

S1 (MH "Blood Platelets")
S2 TI (platelet* or thrombocyte*)
S3 S1 OR S2
S4 (MH "BLOOD TRANSFUSION+")
S5 TI transfus*
S6 S4 or S5
S7 S3 and S6
S8 (MH "PLATELET TRANSFUSION")
S9 (MH PLATELETPHERESIS)
S10 ((platelet* or thrombocyte*) N5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor))
S11 (thrombocytopheres* or plateletpheres*)

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S12 ((platelet* or thrombocyte*) N5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation))
S13 S8 OR S9 OR S10 OR S11 OR S12
S14 (MH "Hematologic Neoplasms+")
S15 (MH Leukemia+)
S16 (MH Lymphoma+)
S17 (MH "Multiple Myeloma+")
S18 (MH "Anemia, Aplastic+")
S19 (MH "Bone Marrow Diseases+")
S20 (MH Thrombocytopenia+)
S21 (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)
S22 ((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*))
S23 (MH "Antineoplastic Agents+")
S24 (MH "Hematopoietic Stem Cell Transplantation")
S25 (MH "Bone Marrow Transplantation")
S26 (MH Radiotherapy+)
S27 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)
S28 ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) N2 patients)
S29 TI (malignan* or oncolog* or cancer*)
S30 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S31 S13 and S30

Appendix 6. TRANSFUSION EVIDENCE LIBRARY search strategy (2015)

#1 ((platelet* OR thrombocyte*) AND (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product OR products OR component* OR concentrate* OR apheres* OR pooled OR single donor OR random donor OR protocol* OR trigger* OR threshold* OR schedul* OR dose OR doses OR dosing OR usage OR utilisation OR utilization))
#2 thrombocytopheres* OR plateletpheres*
#3 #1 OR #2
#4 (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR multiple myeloma OR plasma cell myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR Hodgkin*)
#5 ((haematolog* OR hematolog* OR blood OR red cell* OR white cell* OR lymphom* OR marrow OR platelet*) AND (malignan* OR oncolog* OR cancer OR cancers OR neoplasm*))
#6 #4 OR #5
#7 #3 AND #6

Appendix 7. Web of Science (CPCI-S) search strategy (2015)

((platelet* AND (prophyla* OR transfus* OR products OR component* OR concentrate* OR apheres* OR pooled OR single donor OR random donor OR protocol* OR trigger* OR threshold*)) AND (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic OR myelodysplas* OR myeloproliferat* OR myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR hodgkin* OR haematological OR hematological)) [in Title]
AND (randomized OR randomised OR randomly) [in Title]

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Appendix 8. LILACS search strategy (2015)

((platelet* AND (prophyla* OR transfus* OR products OR component* OR concentrate* OR apheres* OR pooled OR single donor OR random donor OR protocol* OR trigger* OR threshold*)) AND (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic OR myelodysplas* OR myeloproliferat* OR myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR hodgkin* OR haematological OR hematological)) AND db:("LILACS") AND type˙of˙study: ("clinical˙trials" OR "systematic˙reviews")

Appendix 9. INDMED search strategy (2015)

(platelet OR platelets OR thrombocyte$ OR thrombocytopheres$ OR plateletpheres$) AND (thrombocytop$ OR leukemi$ OR leukaemi$ OR lymphoma$ OR aplastic OR myelodysplas$ OR myeloproliferat$ OR myeloma OR thrombocythemi$ OR thrombocythaemi$ OR polycyth$ OR myelofibros$ OR Hodgkin$ OR haematological OR hematological OR hematopoietic OR haematopoietic) AND (random$ OR blind$ OR trial$ OR control$)

Appendix 10. KoreaMed & PakMediNet search strategy (2015)

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

Appendix 11. ClinicalTrials.gov & ICTRP search strategy (2015)

Search Terms/Title: randomized OR randomised
Conditions: hematological neoplasm OR hematological malignancies OR leukemia OR lymphoma OR thrombocytopenia OR multiple myeloma OR aplastic anemia OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkins disease
Intervention: platelets OR platelet transfusion

Appendix 12. ISRCTN & EU Clinical Trials Register search strategy (2015)

(hematological OR haematological OR leukemi* OR leukaemi* OR lymphoma OR thrombocytopeni* OR myeloma OR aplastic OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin*) AND platelet* transfus* AND random*

Appendix 13. Hong Kong Clinical Trials Register search strategy (2015)

Disease Group: Blood and blood-forming organs
Title: randomized OR randomised

Appendix 14. Previous searches: original (Jan 2002) & update (Nov 2011) search strategies

CENTRAL search strategy (Issue 4, 2011)
#1 MeSH descriptor Blood Platelets explode all trees
#2 platelet* or thrombocyte*
#3 (#1 OR #2)
#4 MeSH descriptor Blood Transfusion explode all trees
#5 transfus*
#6 (#4 OR #5)
#7 (#3 AND #6)
#8 MeSH descriptor Platelet Transfusion explode all trees
#9 (platelet* or thrombocyte*) NEAR/5 (transfus* or infus* or administ* or requir*)
#10 (#7 OR #8 OR #9)

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#11 prophylactic* or prophylax* or prevent*
#12 (#10 AND #11)

MEDLINE (Ovid) search strategy (Jan 2002 - Nov 2011)

1. BLOOD PLATELETS/
2. (platelet* or thrombocyte*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.tw.
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. ((platelet* or thrombocyte*) adj5 (transfus* or infus* or administ* or requir*)).tw.
10. or/7-9
11. (prophylactic* or prophylax* or prevent*).tw.
12. 10 and 11

EMBASE (Ovid) search strategy (Jan 2002 - Nov 2011)

1. THROMBOCYTE/
2. (platelet* or thrombocyte*).tw.
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.tw.
6. 4 or 5
7. 3 and 6
8. THROMBOCYTE TRANSFUSION/
9. ((platelet* or thrombocyte*) adj5 (transfus* or infus* or administ* or requir*)).tw.
10. or/7-9
11. (prophylactic* or prophylax* or prevent*).tw.
12. 10 and 11

CINAHL (NHS Evidence) search strategy (Jan 2002 - Nov 2011)

1. BLOOD PLATELETS/
2. (platelet* or thrombocyte*).ti,ab
3. 1 or 2
4. exp BLOOD TRANSFUSION/
5. transfus*.ti,ab
6. 4 or 5
7. 3 and 6
8. PLATELET TRANSFUSION/
9. ((platelet* adj5 transfus*) or (platelet* adj5 infus*) or (platelet* adj5 administ*) or (platelet* adj5 requir*)).ti,ab
10. ((thrombocyte* adj5 transfus*) or (thrombocyte* adj5 infus*) or (thrombocyte* adj5 administ*) or (thrombocyte* adj5 requir*)).ti,ab
11. 7 or 8 or 9 or 10
12. (prophylactic* or prophylax* or prevent*).ti,ab
13. 11 and 12

Free text search strategy for other databases (Nov 2011)

(platelet* OR thrombocyte*) AND (transfus* OR infus* OR administ* OR requir*) AND (prophylactic* OR prophylaxis OR prevent OR prevention OR preventing)

MEDLINE & EMBASE search strategy (Jan 2002)

1. Platelet Transfusion.mh.
2. platelet$ adj10 (substitute$ or transfusion$ or prophyla$).tw.
3. 1 or 2
4. haemorrhage.mh.
5. platelet$.tw.
6. 4 and 5

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7. exp Blood Transfusion/
8. 5 and 7
9. 3 or 6 or 8

WHAT'S NEW

Last assessed as up-to-date: 23 July 2015.

Date	Event	Description
23 July 2015	New search has been performed	Updated search, no new studies identified.
6 March 2014	New citation required but conclusions have not changed	The previous review, Estcourt 2012a, has now been split into four separate reviews. Protocols have been published for these four separate reviews (Estcourt 2014a; Estcourt 2014b; Estcourt 2014c; Estcourt 2014d). Two new outcomes have been added to the protocol (platelet transfusion interval, quality of life) (Estcourt 2014c). The primary and secondary outcomes have been reported over time-frames prespecified within the protocol (Estcourt 2014c). The platelet threshold comparisons have been prespecified.

CONTRIBUTIONS OF AUTHORS

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

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

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

Sally Hopewell: protocol development and methodological expert.

Marialena Trivella: protocol development and statistical expert.

Mike Murphy: protocol development and content expert.

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DECLARATIONS OF INTEREST

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

Simon Stanworth: none declared.

Carolyn Doree: none declared.

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For technical systematic review support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The previous review, Estcourt 2012a, has now been split into four separate reviews. Protocols were published for these four separate reviews (Estcourt 2014a; Estcourt 2014b; Estcourt 2014c; Estcourt 2014d). There have been no changes between the protocol for this review, Estcourt 2014c, and the completed review.

Aspects of the protocol that were not implemented due to lack of data

We did not perform a formal assessment of potential publication bias (small-trial bias) because the review included fewer than 10 trials (Sterne 2011).

We did not prespecify in the protocol how we would deal with any unit of analysis issues. For this review there was a unit of analysis issue for the total number of days of bleeding. We only reported the number of days of bleeding if it had been reported per participant, or if the authors had performed an appropriate analysis to account for repeated measures. In this review, the Rebulla 1997 authors used a permutation analysis according to Freedman 1989 to take into account the repeated events data; all other studies did not take into account unit of analysis issues with this outcome, and so data were not reported.

We could not perform three of the four planned comparisons, because no included study compared these interventions.

- No studies compared a lower platelet count threshold (5 x 10^9/L) versus a standard platelet transfusion threshold (10 x 10^9/L).
- No studies compared different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that did not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L).
- No studies compared alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number).

Secondary outcomes: None of the studies reported on the platelet transfusion interval; additional interventions to stop bleeding; transfusion-transmitted infection; or quality of life.

Subgroup analyses: We did not perform two subgroup analyses due to lack of data; these were presence of fever and type of treatment. We did not perform meta-regression because no subgroup contained more than 10 studies (Deeks 2011). We commented on differences between subgroups as a narrative.

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Assessment of heterogeneity: We did not assess age of study as a reason for heterogeneity, as all studies recruited participants between 1991 and 2001.
Sensitivity analyses: None of the three included trials had more that 20% of participants lost to follow-up, and all of the trials had some threats to validity, therefore we performed neither pre-planned sensitivity analysis.

NOTES

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

Part of the methods section of this review is based on a standard template established by the Haematological Malignancies Group.

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