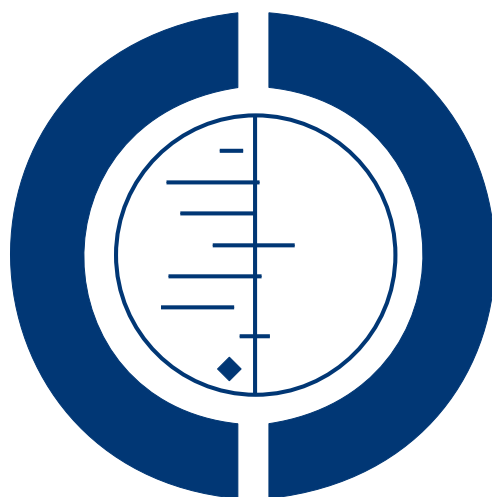


A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation (Review)

Crighton GL, Estcourt LJ, Wood EM, Trivella M, Doree C, Stanworth S



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A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients 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 thrombocytopenic patients with 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 updated in 2012 that addressed four separate questions: therapeutic-only versus prophylactic platelet transfusion policy; prophylactic platelet transfusion threshold; prophylactic platelet transfusion dose; and platelet transfusions compared to alternative treatments. We have now split this review into four smaller reviews looking at these questions individually; this review is the first part of the original review.

Objectives

To determine whether a therapeutic-only platelet transfusion policy (platelet transfusions given when patient bleeds) is as effective and safe as a prophylactic platelet transfusion policy (platelet transfusions given to prevent bleeding, usually when the platelet count falls below a given trigger level) in patients with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation.

Search methods

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

A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation (Review)

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Selection criteria

RCTs involving transfusions of platelet concentrates prepared either from individual units of whole blood or by apheresis, and given to prevent or treat bleeding in patients with malignant haematological disorders receiving myelosuppressive chemotherapy or undergoing HSCT.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

We identified seven RCTs that compared therapeutic platelet transfusions to prophylactic platelet transfusions in haematology patients undergoing myelosuppressive chemotherapy or HSCT. One trial is still ongoing, leaving six trials eligible with a total of 1195 participants. These trials were conducted between 1978 and 2013 and enrolled participants from fairly comparable patient populations. We were able to critically appraise five of these studies, which contained separate data for each arm, and were unable to perform quantitative analysis on one study that did not report the numbers of participants in each treatment arm.

Overall the quality of evidence per outcome was low to moderate according to the GRADE approach. None of the included studies were at low risk of bias in every domain, and all the studies identified had some threats to validity. We deemed only one study to be at low risk of bias in all domains other than blinding.

Two RCTs (801 participants) reported at least one bleeding episode within 30 days of the start of the study. We were unable to perform a meta-analysis due to considerable statistical heterogeneity between studies. The statistical heterogeneity seen may relate to the different methods used in studies for the assessment and grading of bleeding. The underlying patient diagnostic and treatment categories also appeared to have some effect on bleeding risk. Individually these studies showed a similar effect, that a therapeutic-only platelet transfusion strategy was associated with an increased risk of clinically significant bleeding compared with a prophylactic platelet transfusion policy. Number of days with a clinically significant bleeding event per participant was higher in the therapeutic-only group than in the prophylactic group (one RCT; 600 participants; mean difference 0.50, 95% confidence interval (CI) 0.10 to 0.90; moderate-quality evidence). There was insufficient evidence to determine whether there was any difference in the number of participants with severe or life-threatening bleeding between a therapeutic-only transfusion policy and a prophylactic platelet transfusion policy (two RCTs; 801 participants; risk ratio (RR) 4.91, 95% CI 0.86 to 28.12; low-quality evidence). Two RCTs (801 participants) reported time to first bleeding episode. As there was considerable heterogeneity between the studies, we were unable to perform a meta-analysis. Both studies individually found that time to first bleeding episode was shorter in the therapeutic-only group compared with the prophylactic platelet transfusion group.

There was insufficient evidence to determine any difference in all-cause mortality within 30 days of the start of the study using a therapeutic-only platelet transfusion policy compared with a prophylactic platelet transfusion policy (two RCTs; 629 participants). Mortality was a rare event, and therefore larger studies would be needed to establish the effect of these alternative strategies. There was a clear reduction in the number of platelet transfusions per participant in the therapeutic-only arm (two RCTs, 991 participants; standardised mean reduction of 0.50 platelet transfusions per participant, 95% CI -0.63 to -0.37; moderate-quality evidence). None of the studies reported quality of life. There was no evidence of any difference in the frequency of adverse events, such as transfusion reactions, between a therapeutic-only and prophylactic platelet transfusion policy (two RCTs; 991 participants; RR 1.02, 95% CI 0.62 to 1.68), although the confidence intervals were wide.

Authors' conclusions

We found low- to moderate-grade evidence that a therapeutic-only platelet transfusion policy is associated with increased risk of bleeding when compared with a prophylactic platelet transfusion policy in haematology patients who are thrombocytopenic due to myelosuppressive chemotherapy or HSCT. There is insufficient evidence to determine any difference in mortality rates and no evidence of any difference in adverse events between a therapeutic-only platelet transfusion policy and a prophylactic platelet transfusion policy. A therapeutic-only platelet transfusion policy is associated with a clear reduction in the number of platelet components administered.

PLAIN LANGUAGE SUMMARY

Platelet transfusions to treat bleeding compared with platelet transfusions to prevent bleeding in people with blood cancers receiving intensive treatment

A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation (Review)

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Review question

We evaluated the evidence regarding whether giving platelet transfusions to patients with low platelets who are bleeding (therapeutically) is as effective and safe as giving platelet transfusions regularly to prevent bleeding (prophylactically). Our target population was people with blood cancers who were receiving intensive myelosuppressive (causing decreased blood cell production) chemotherapy treatments or stem cell transplantation.

Background

People with blood cancers may have low platelet counts because of their underlying cancer. Blood cancers may be treated with chemotherapy and stem cell transplantation, which can cause low platelet counts. Platelet transfusions may be given when the platelet count falls below a prespecified platelet count (for example $10 \times 10^9/L$) to prevent bleeding, or they may be given to treat bleeding (such as a prolonged nosebleed or multiple bruises). The routine use of platelet transfusions to prevent bleeding in these patients has not previously been supported by high-quality evidence.

Study characteristics

The evidence is current to July 2015. In this update, we identified seven randomised controlled trials that compared only giving platelet transfusions to treat bleeding versus giving platelet transfusions to prevent and treat bleeding. One trial is still recruiting participants and has not been completed. We reviewed six randomised controlled trials with a total of 1195 participants. These trials were conducted between 1978 and 2013. Five of the trials included adults who were receiving chemotherapy or a stem cell transplantation as treatment for blood cancers. One of the trials included children receiving chemotherapy for leukaemia.

Four of the six studies reported funding sources; these were charitable foundations or government funds.

Key results

Giving platelet transfusions to prevent and treat bleeding in patients with low platelet counts due to blood cancers or their treatments may result in a reduction in bleeding when compared with giving platelet transfusions only to treat bleeding.

There may not be an increased risk of death or adverse events if platelet transfusions are only given to treat bleeding versus giving platelet transfusions to prevent and treat bleeding, but there was not enough evidence to be certain about this.

Giving platelet transfusions only when bleeding occurs probably reduces the number of platelets given.

None of the six studies reported any quality-of-life outcomes.

Quality of the evidence

The evidence for most of the findings was of low or moderate quality, as patients and their doctors knew which study arm the patient had been put in; outcomes reported in the studies were difficult to compare because bleeding was measured and reported differently; and some outcomes were imprecise, because the outcome did not happen very often (such as death).

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

Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation						
Patient or population: patients with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation Settings: Hospital inpatient or outpatient setting Intervention: a therapeutic-only platelet transfusion policy Comparison: a prophylactic platelet transfusion policy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk					
	Prophylactic platelet transfusion policy	Therapeutic-only platelet transfusion policy				
Number of participants with at least 1 bleeding episode up to 30 days from study entry Modified WHO grading scale	Not estimable	Not estimable	Not estimable	801 (2 studies)	See comment	An estimate of the level of effect could not be made due to differences in the way bleeding was assessed in the 2 studies. A higher proportion of participants had WHO Grade 2 or above bleeding in the therapeutic-only policy arms in both studies
Number of days with significant bleeding per participant up to 30 days from study entry Modified WHO grading scale	-	The mean number of days with significant bleeding per participant in the intervention groups was 0.5 higher (0.1 to 0.9 higher)	-	599 (1 study)	⊕⊕⊕○ moderate ¹	Only 1 study reported this outcome over a 30 day follow-up period (Stanworth 2013)

Number of participants with severe or life-threatening bleeding up to 30 days from study entry Modified WHO grading scale	Study population		RR 4.91 (0.86 to 28.12)	801 (2 studies)	⊕⊕○○ low ^{1,2}	
	3 per 1000	10 per 1000 (3 to 71)				
	Moderate					
	2 per 1000	8 per 1000 (2 to 56)				
Time to first bleeding episode up to 30 days from study entry	Not estimable	Not estimable	Not estimable	801 (2 studies)	See comment	An estimate of the level of effect could not be made due to differences in the way bleeding was assessed in the 2 studies. The time to first WHO Grade 2 or above bleeding episode was shorter in the therapeutic-only policy arms in both studies
Mortality from all causes up to 30 days from study entry	Not estimable	Not estimable	Not estimable	629 (2 studies)	See comment	Only 1 of these 2 studies reported any deaths in either study arm (Stanworth 2013). There were 5 deaths in the therapeutic arm (301 participants) and 4 deaths in the prophylactic arm (299 participants)
Number of platelet transfusions per participant up to 30 days from study entry		The mean number of platelet transfusions per participant in the intervention groups was 0.50 lower (0.63 to 0.37 lower)		801 (2 studies)	⊕⊕⊕○ moderate ¹	

Quality of life - not reported	Not estimable	Not estimable	0 (0 studies)	See comment	None of the 6 studies reported any quality-of-life outcomes
<p>*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).</p> <p>CI: Confidence interval; RR: Risk ratio; WHO: World Health Organization</p>					
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>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.</p> <p>Very low quality: We are very uncertain about the estimate.</p>					

¹ We downgraded the quality of evidence by 1 for risk of performance bias and detection bias, due to the lack of blinding.

² We downgraded the quality of evidence by 1 for imprecision due to wide confidence intervals of the pooled estimates and individual trials contributing to this outcome.

BACKGROUND

Description of the condition

Haematological malignancies account for between 8% and 9% of all new cancers reported in the UK and US (CDC 2012; ONS 2012), and their incidence is increasing (11% to 14% increase in new cases of lymphoma and myeloma between 1991 to 2001 and 2008 to 2010) (Cancer Research UK 2013). The prevalence of haematological malignancies is also increasing due to increased survival rates (Coleman 2004; Rachet 2009), which are the result of the introduction of myelosuppressive chemotherapy treatments and use of stem cell transplantation (Burnett 2011; Fielding 2007; Patel 2009). Over 50,000 haematopoietic stem cell transplants (HSCTs) are carried out annually worldwide 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, myelosuppressive chemotherapy and HSCT 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 HSCT. The ready availability of platelet concentrates in many countries has undoubtedly made a major contribution in allowing the development of intensive treatment regimens for haematological disorders (malignant and non-malignant) and other malignancies. The first demonstration of the effectiveness of platelet transfusions was performed in 1910 (Duke 1910). However, it was not until the 1970s and 1980s that the use of platelet transfusions became standard treatment for thrombocytopenic patients with bone marrow failure (Blajchman 2008). Alongside changes in supportive care, the routine use of platelet transfusions in patients with haematological disorders since that time has led to a marked decrease in the number of haemorrhagic deaths associated with thrombocytopenia (Slichter 1980). This has resulted in a considerable increase in the demand for platelet concentrates. Currently, platelet concentrates are the second most frequently used blood component. Administration of platelet transfusions to patients with haematological disorders now 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).

Patients can become refractory to platelet transfusions. In an analysis of the TRAP 1997 study data, there was a progressive decrease in the post-transfusion platelet count increments and time interval between transfusions as the number of preceding transfusions increased (Slichter 2005). This effect was seen irrespective of whether the patient developed detectable human leukocyte antigen (HLA) antibodies (Slichter 2005).

Platelet transfusions are also associated with adverse events. Mild to moderate reactions to platelet transfusions include rigors, fever, and urticaria (Heddle 2009b). These reactions are not life-threatening, but 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 2010; Knowles 2011; Pearce 2011; Popovsky 1985; Silliman 2003).

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

Description of the intervention

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

This review did not focus on the absolute need for platelet transfusions in this patient population, but instead on whether a prophylactic platelet transfusion policy is required. The standard practice in most haematology units in high-income countries is to use prophylactic transfusions, in line with guidelines (BCSH 2003; BCSH 2004; Board 2009; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007). The experimental intervention will be to give platelet transfusions only when bleeding occurs (therapeutic-only strategy).

How the intervention might work

Prophylactic versus therapeutic-only platelet transfusions

A retrospective review of almost 3000 thrombocytopenic adult patients over a 10-year period showed no relationship between the first morning platelet count, or the lowest platelet count of the day, and the risk of severe or life-threatening bleeding (World Health Organization (WHO) Grade 3 to 4 bleeding) (Friedmann 2002). This raised the question as to whether a threshold-defined prophylactic platelet transfusion approach is appropriate. Further large studies have confirmed this finding and also shown no relationship between the morning platelet count and the risk of clinically significant bleeding (WHO Grade 2 bleeding) the following day except

at very low platelet counts ($\leq 5 \times 10^9/L$) (Slichter 2010; Wandt 2012). Further support for the absence of a relationship between the severity of thrombocytopenia and bleeding came from a review of case reports of severe intracranial haemorrhage, which found no clear evidence for an association between the occurrence of major intracranial bleeding and absolute platelet count just prior to the onset of severe bleeding (Stanworth 2005). Thus, the overall benefit of a prophylactic platelet transfusion policy over a policy to give platelets therapeutically only, using a platelet count threshold, has not been established. A recent trial suggested that a therapeutic-only platelet transfusion policy might become the new standard of care in selected patients, however the primary endpoint for this study was a reduction in the number of platelet transfusions, rather than a clinical outcome such as bleeding (Wandt 2012). The Trial of Platelet Prophylaxis (TOPPS) is another large RCT that has been recently completed and may provide additional evidence (Stanworth 2010; Stanworth 2012).

Assessment of bleeding

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

Any review that uses bleeding as a primary outcome measure needs to assess the way that the trials have recorded bleeding. Unfortunately, bleeding assessment and recording have 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 that are based on the WHO system is that the categories are relatively broad and subjective. This means that a small change in a patient's bleeding risk may not be detected. Another limitation is that the modified WHO categories are partially defined by whether a bleeding patient requires a blood transfusion. The threshold for intervention may vary between clinicians and institutions, and so the same level of bleeding could be graded differently in different institutions.

The definition of what constitutes clinically significant bleeding has varied between studies. Although the majority of more recent platelet transfusion studies now classify it as WHO Grade 2 or above (Heddle 2009a; Slichter 2010; Stanworth 2012; Wandt 2012), there has been greater heterogeneity in the past (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.

Why it is important to do this review

Considerable advances have been made in platelet transfusion therapy in the last 40 years. However, three 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, is a therapeutic-only platelet transfusion strategy as effective and safe as a prophylactic platelet transfusion policy for the prevention or control (or both) of life-threatening bleeding in this setting?

The initial formulation of this Cochrane review attempted to answer these questions, but there was insufficient evidence available at the time for us to draw any definitive conclusions (Stanworth 2004). Although the original review was recently updated (Estcourt 2012a), it is now outdated because two new large studies have recently been completed (Stanworth 2012; Wandt 2012). Sufficient additional information regarding these different questions now exists. For clarity and simplicity, we have split the review to answer each question separately.

This review will focus solely on the third question: Is a therapeutic-only platelet transfusion strategy as effective and safe as a prophylactic platelet transfusion policy for the prevention or control (or both) of life-threatening bleeding in the setting of thrombocytopenia?

We will assess the other two questions in two separate reviews, with an additional third review assessing the use of alternative agents instead of prophylactic platelet transfusions.

Avoiding the need for unnecessary prophylactic platelet transfusions in patients with haematologic malignancies will have significant logistical and financial implications for national health services as well as decreasing patients' exposure to the risks of transfusion. This knowledge is perhaps even more important in the development of platelet transfusion strategies in low-income countries, where access to blood components is much more limited (Verma 2009).

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

OBJECTIVES

To determine whether a therapeutic-only platelet transfusion policy (platelet transfusions given when patient bleeds) is as effective and safe as a prophylactic platelet transfusion policy (platelet transfusions given to prevent bleeding, usually when the platelet count falls below a given trigger level) in patients with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation (Estcourt 2014d).

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of interventions

Participants in both treatment arms received transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis to treat bleeding (therapeutic platelet transfusions). Participants in the control arm also received prophylactic platelet transfusions. Prophylactic platelet transfusions are typically given when the platelet count falls below a given threshold. There was no restriction on the dose, frequency, type of platelet component, or transfusion trigger of the platelet transfusions, but where it was available we took this information into account in the analysis.

We included the following comparisons:

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

Types of outcome measures

Primary outcomes

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

1. The number of participants with at least one bleeding episode.
2. The total number of days on which bleeding occurred per participant.
3. The number of participants with at least one episode of severe or life-threatening bleeding.
4. Time to first bleeding episode from the start of the 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.
 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, cryoprecipitate) within 30 days from the start of the study.
 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. The 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 and 90 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. We planned to report the following two of our outcomes as a narrative:
- Assessment of quality of life, as there is no definitive patient-reported outcome measure for this patient group (Estcourt 2014e).

- Platelet transfusion interval, which can be calculated in many different ways, and we expected that the exact methodology would not be reported sufficiently to allow us to combine the data.

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

Search methods for identification of studies

The Systematic Review Initiative 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:

- CENTRAL (Cochrane Library 2015, Issue 6, 23 July 2015) (Appendix 1)
- MEDLINE (OvidSP, 1946 to 23 July 2015) (Appendix 2)
- PubMed (publications only, on 23 July 2015) (Appendix 3)
- Embase (OvidSP, 1974 to 23 July 2015) (Appendix 4)
- CINAHL (EBSCOhost, 1937 to 23 July 2015) (Appendix 5)
- 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 23 July 2015) (Appendix 8)
- IndMed (ICMR-NIC, 1986 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 (version 1) in January 2002, Stanworth 2004, and the updated search (version 2) in November 2011, Estcourt 2012a. We did not re-screen the original search strategies and instead placed date restrictions from the date of the final search in the preceding review (10 November 2011) to 23 July 2015 for four databases included in version 2 of the review (CENTRAL, MEDLINE, Embase and CINAHL). The other databases had no date restrictions.

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).

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.

We have presented all new search strategies as indicated in Appendices 1 to 13. We have presented search strategies for both the version 1 (2002) and version 2 (2011) searches 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.

Data collection and analysis

Selection of studies

We updated the selection of studies from the selection of studies performed for the update (version 2) of this review (Estcourt 2012a).

Two out of three independent review authors (GC and LE) or (LE 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 review authors (GC, LE) independently formally assessed the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We resolved all disagreements by discussion without needing to consult a third review author (SS). We sought further information from study authors if the 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 two groups could be defined in the trial on the basis of a therapeutic-

only versus prophylactic platelet transfusion strategy. We recorded the reasons for excluding potentially relevant studies.

Data extraction and management

We updated the data extraction from the data extraction performed for the previous version of this review (Estcourt 2012a). This included data extraction for all new studies included since the previous review and also for all review outcomes that were not part of the previous review (for example platelet transfusion interval, quality of life).

Two review authors (GC, LE) conducted the data extraction according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011a). Potential 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 were piloted in the previous version of this review (Estcourt 2012a). Due to minor changes in the format, the forms were piloted on a further study; thereafter, the two review authors (GC, LE) independently extracted data for all the studies. The following data were extracted.

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.
- Time to first bleeding episode.
- 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, e.g. tranexamic acid; other blood products, e.g. fresh frozen plasma, cryoprecipitate).
- Quality of life.
- Adverse effects of treatments (e.g. 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. Where these sources provided insufficient information, we contacted authors and study groups for additional details.

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

Assessment of risk of bias in included studies

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

Two review authors (GC, LE) assessed all newly included studies for possible risk of bias (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c)). The assessment included information about the design, conduct, and analysis of the trial. We evaluated each criterion on a three-point scale: low risk of bias, high risk of bias, or unclear. To assess risk of bias, we included 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 each 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?
- Was the protocol deviation balanced between treatment arms?

Measures of treatment effect

For dichotomous outcomes, we recorded the number of outcomes in treatment and control groups and estimated the treatment effect measures across individual studies as the relative effect measures (risk ratio (RR) 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](#).

If appropriate, we reported the number needed to treat to benefit with CIs and the number needed to treat to harm with CIs.

If we could not report the data available 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. In one study ([Wandt 2012](#)), there were unit of analysis issues for the study's secondary outcomes. Some outcomes were reported per treatment cycle rather than per participant, and some participants received more than one cycle of chemotherapy. We resolved this by only using data within meta-analyses for participants who had received only one cycle of treatment (autologous stem cell transplant patients). We have requested data from the author so that we can include data on all participants within a subsequent review. The study's primary outcome adjusted for repeated courses of chemotherapy ([Wandt 2012](#)).

We did not prespecify in the protocol how we would deal with multi-arm studies. One study, [Grossman 1980](#), was a factorial RCT and included four arms: 1) therapeutic (T)/blood bank (BB)/random-donor platelets, 2) T/single donor (SD), 3) prophylactic (P)/BB and 4) P/SD. For our study outcomes of interest, aggregate data comparing the therapeutic and prophylactic were provided by the author.

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, of which two authors supplied missing data ([Grossman 1980](#); [Stanworth 2013](#)). One author searched for missing data but it was no longer available

([Sintnicolaas 1982](#)). One author has agreed to provide additional data; this data is not yet available and will be incorporated into the next version of this review ([Wandt 2012](#)).

In trials that included participants with haematological disorders as well as participants with solid tumours or non-malignant haematological disorders, we extracted data for the haematology subgroup that was receiving myelosuppressive chemotherapy or stem cell transplantation from the general trial data.

When data were missing within an outcome, the preferred analysis was intention-to-treat analysis. 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 Chi² test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify possible heterogeneity (I^2 greater than 50%, moderate heterogeneity; I^2 greater than 80%, considerable heterogeneity). We explored potential causes of heterogeneity by sensitivity and subgroup analyses if possible.

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias (small-trial bias) by generating a funnel plot and statistically test using a linear regression test ([Sterne 2011](#)), because the review included fewer than 10 trials.

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 employed 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.

We used GRADEprofiler [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; 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, overall mortality at 30 days, and quality of life.

Subgroup analysis and investigation of heterogeneity

Two subgroup analyses were prespecified in the previous version of this review (Estcourt 2012a): fever and participants' diagnostic and treatment subgroups. We considered performing subgroup analysis on the following prespecified characteristics, if appropriate:

- Presence of fever ($> 38^{\circ}\text{C}$).
- Underlying disease.
- Type of treatment (autologous HSCT, allogeneic HSCT, or chemotherapy alone).
- Age of the participant (paediatric, adults, older adults (> 60 years)).

Due to lack of data, we performed only three of these subgroup analyses; underlying disease, type of treatment, and age of participant.

We did not perform meta-regression because no subgroup contained more than 10 studies (Deeks 2011). We commented on differences between subgroups as narrative.

We also included investigation of heterogeneity between studies, if appropriate:

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

Four of the six included studies (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Solomon 1978), all conducted in the 1970s and 1980s, compared prophylactic platelet transfusions with a platelet count threshold of $20 \times 10^9/\text{L}$, whilst the two more recent studies, Stanworth 2013 and Wandt 2012, used a platelet count threshold

of $10 \times 10^9/\text{L}$ for prophylactic platelet transfusions. We did not perform assessment of heterogeneity between studies due to the lack of standardised reporting of outcomes.

Sensitivity analysis

We had intended to assess the robustness of our findings by performing 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 six included RCTs were blinded.

None of the six included trials had more than 20% of participants lost to follow-up.

We therefore did not perform these two sensitivity analyses.

RESULTS

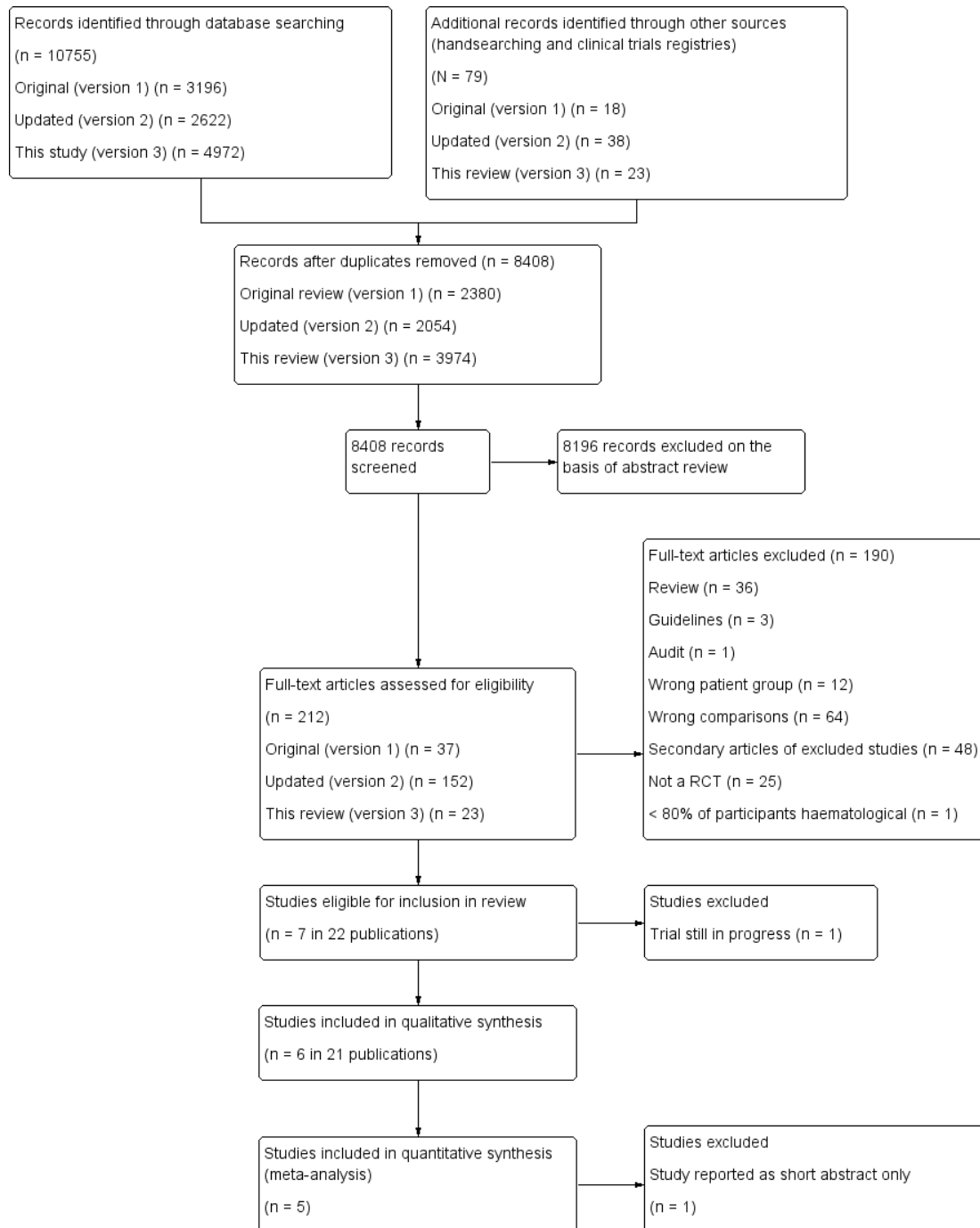
Description of studies

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

Results of the search

See PRISMA flow diagram (Figure 1). The original search (conducted January 2002) identified a total of 3196 potentially relevant citations. There were 2380 citations after duplicates were removed, and one review author could exclude 2343 records 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).

Figure 1. PRISMA flow diagram for original review (1950 to January 2002), updated search (January 2002 to November 2011), and current review (November 2011 to 23 July 2015)



The updated search (conducted November 2011) identified a total of 2622 potentially relevant citations. There were 2054 citations after duplicates were removed, and two review authors could exclude 1865 records on the basis of the abstract. In this review, we retrieved 152 full-text articles for relevance. Two review authors reviewed these full-text articles and those from the original review (a total of 189 citations).

This search (conducted 23 July 2015) identified a total of 4972 potentially relevant citations. There were 3974 citations after duplicates were removed, and any two of three review authors (LE, GC, CD) could exclude 3951 records on the basis of the abstract. Two review authors (LE, GC) retrieved for relevance and reviewed 23 full-text articles.

The previous systematic review, [Estcourt 2012a](#), identified five trials that compared therapeutic-only platelet transfusions versus prophylactic platelet transfusions, three completed trials, [Murphy 1982](#), [Sintnicolaas 1982](#), and [Solomon 1978](#), and two ongoing studies, [Stanworth 2013](#) and [Wandt 2012](#), which are now included. This search identified two additional studies ([Grossman 1980](#); [NCT01615146](#)). The study by [Grossman 1980](#) was not identified in the previous systematic review ([Estcourt 2012a](#)), because the study was only published as an abstract, and had not been identified via handsearching conference proceedings in the original review ([Stanworth 2004](#)). The study was identified via an electronic search after it had been added to the database of the Transfusion Evidence Library (www.transfusionevidencelibrary.com). We identified no studies that compared prophylactic platelet transfusions with placebo.

In total, seven studies were assessed and deemed eligible for inclusion ([Grossman 1980](#); [Murphy 1982](#); [NCT01615146](#); [Sintnicolaas 1982](#); [Solomon 1978](#); [Stanworth 2013](#); [Wandt 2012](#)). Findings of the [NCT01615146](#) have yet to be published.

Included studies

See [Characteristics of included studies](#) for full details of each study. Seven studies were eligible for inclusion; one of these studies is ongoing ([NCT01615146](#)).

The six remaining RCTs (21 publications) were published between 1978 and 2013. There were 15 secondary citations of included studies (cited as secondary references for the relevant included studies). Three studies were included in the original review ([Murphy 1982](#); [Sintnicolaas 1982](#); [Solomon 1978](#)), and three new studies have been added to this update review ([Grossman 1980](#); [Stanworth 2013](#); [Wandt 2012](#)).

[Sintnicolaas 1982](#) was only reported as a short abstract, and no further information was available from the author, therefore we excluded this study from any quantitative analysis (12 participants were randomised, but the numbers in each arm of the study were not stated). [Grossman 1980](#) was originally published in short ab-

stract form; the author provided a copy of their final unpublished manuscript. Data presented in the review is from both the abstract and unpublished manuscript.

See [Table 1](#) for study characteristics, including number and type of participants, type of intervention, duration of study, type of platelet product, and primary outcome.

Design

All six studies were open-label studies. There were three single-centre parallel RCTs ([Murphy 1982](#); [Sintnicolaas 1982](#); [Solomon 1978](#)), one factorial RCT ([Grossman 1980](#)), and two multi-centre parallel RCTs ([Stanworth 2013](#); [Wandt 2012](#)).

Sample sizes

The number of participants randomised ranged from 12 in [Sintnicolaas 1982](#) to 600 in [Stanworth 2013](#).

Setting

Four studies were conducted in the 1970s and 1980s ([Grossman 1980](#); [Murphy 1982](#); [Sintnicolaas 1982](#); [Solomon 1978](#)), and two studies were conducted in the mid- to late 2000s ([Stanworth 2013](#); [Wandt 2012](#)). Two studies were conducted in the United States ([Murphy 1982](#); [Solomon 1978](#)), one in Canada ([Grossman 1980](#)), one in the Netherlands ([Sintnicolaas 1982](#)), one in Germany ([Wandt 2012](#)), and one in both Australia and the United Kingdom ([Stanworth 2013](#)).

Participants

The previous systematic review included a total of 99 participants. This review now includes a total of 1195 participants randomised to receive either therapeutic-only or prophylactic platelet transfusions. Of these 1195 participants, we included only 1186 in the analysis. [Solomon 1978](#) excluded two participants because they died from an intracranial haemorrhage on the first day of the study. [Stanworth 2013](#) excluded two participants from analysis as they were lost to follow-up, and [Wandt 2012](#) excluded four participants from the analysis because they did not receive the allocated intervention, and one was lost to follow-up.

Study populations varied slightly between studies but were fairly comparable. Five of the six studies enrolled adults with a haematological malignancy ([Grossman 1980](#); [Sintnicolaas 1982](#); [Solomon 1978](#); [Stanworth 2013](#); [Wandt 2012](#)), whilst one study enrolled paediatric patients with acute leukaemia ([Murphy 1982](#)). Three of the six studies only included participants with acute leukaemia (acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL), or both) ([Murphy 1982](#); [Sintnicolaas 1982](#);

Solomon 1978). The three other studies also included people with other haematological disorders who were either thrombocytopenic or expected to become thrombocytopenic for at least five days or who were undergoing an HSCT (Grossman 1980; Stanworth 2013; Wandt 2012).

Studies' exclusion criteria

Four of the six studies reported exclusion criteria (Grossman 1980; Solomon 1978; Stanworth 2013; Wandt 2012). Three of these four studies excluded people with specific types of leukaemia. Two studies excluded people with acute promyelocytic leukaemia (APML) (Solomon 1978; Stanworth 2013), whilst Wandt 2012 only included people with APML who were in complete remission. Three of these four studies excluded people with platelet refractoriness (Grossman 1980; Stanworth 2013; Wandt 2012). Two of these four studies excluded participants who were not candidates for aggressive therapy (Grossman 1980; Stanworth 2013), whereas Wandt 2012 only included people who were enrolled in specific leukaemia trials or were receiving an autologous HSCT. Two of these four studies excluded participants if they were not expected to have prolonged thrombocytopenia (at least five days with a platelet count $\leq 50 \times 10^9/L$) (Grossman 1980; Stanworth 2013). Two of these four studies excluded people with a known history of clinically significant bleeding, a haemostatic or coagulation disorder (Stanworth 2013; Wandt 2012). One of the four studies excluded participants in the autologous HSCT group who had pulmonary or cerebral lesions and participants with light-chain amyloidosis (Wandt 2012). One of these four studies excluded participants who required treatment with regular antiplatelet agents or anticoagulants (Stanworth 2013). One of these four studies excluded women who were pregnant (Stanworth 2013).

Intervention

Four of the six studies (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Solomon 1978), all conducted in the 1970s and 1980s, compared prophylactic platelet transfusions with a platelet count threshold of $20 \times 10^9/L$ versus a therapeutic-only platelet transfusion regimen (platelet transfusions given for clinically significant bleeding). In two of these four studies, platelet transfusions were also given in the therapeutic arm for specific indications (Grossman 1980; Solomon 1978). In Solomon 1978, platelet transfusions were also given in the therapeutic ("specific indications") arm if there had been a 50% fall in platelets to below $20 \times 10^9/L$ over the previous 24 hours. In Grossman 1980, platelet transfusions were also given in the therapeutic arm prior to invasive procedures. The two more recent studies, Stanworth 2013 and Wandt 2012, used a platelet count threshold of $10 \times 10^9/L$ for prophylactic platelet transfusions and gave therapeutic platelet transfusions for clinically relevant bleeding, defined as WHO Grade 2 or higher. Stanworth 2013 specified that platelet

transfusions would be given to both groups prior to planned invasive procedures, and could also be given at the physician's discretion (the most common reason was because patients were septic or unwell). Wandt 2012 specified that prophylactic platelet transfusions would be given to the therapeutic group at a threshold platelet count of $10 \times 10^9/L$ when there was an increased bleeding risk due to associated coagulopathy, sepsis, or infection.

Five of the six studies defined the platelet dose (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Stanworth 2013; Wandt 2012), however the platelet dose definition varied between studies. Two studies defined a therapeutic or prophylactic platelet dose as a single adult platelet unit (Stanworth 2013; Wandt 2012). In Murphy 1982, the platelet dose was 4 units/ m^2 , and in Sintnicolaas 1982 the dose was 4×10^{11} /unit. Grossman 1980 reported an average dose for the random-donor group of 5.44×10^{11} platelets/unit and 4.8×10^{11} platelets/unit in the single-donor group.

The type of platelet product varied between studies. Sintnicolaas 1982 did not specify the type of platelet product. Murphy 1982 and Solomon 1978 used pooled random-donor platelets. Stanworth 2013 and Wandt 2012 used both apheresis and pooled platelet components. Grossman 1980 specifically set out to compare both single-donor and blood bank (random-donor) platelets between the therapeutic-only and prophylactic arms.

Co-interventions

Two of the six studies reported a red cell transfusion policy (Stanworth 2013; Wandt 2012). Wandt 2012 transfused participants to maintain a haemoglobin concentration at 80 g/L or higher, whilst Stanworth 2013 used a haemoglobin threshold of 90 g/L in the absence of blood loss due to bleeding.

One of the six studies was a factorial study with four treatment arms (Grossman 1980). Participants were randomised to receive random-donor versus single-donor platelet components, as well as a therapeutic-only versus prophylactic platelet transfusion strategy. None of the studies reported any other co-interventions.

Outcomes

Studies contributing to the main outcomes

See *Effects of interventions* for the number of studies that report each review outcome.

Three of the six studies reported a primary outcome (Murphy 1982; Stanworth 2013; Wandt 2012). The primary outcome for Murphy 1982 was survival, whilst the primary endpoint for Wandt 2012 was the number of platelet transfusions given during the study observation period of 14 days. In contrast, the primary outcome for Stanworth 2013 was the proportion of participants who experienced WHO Grade 2, 3, or 4 bleeding events up to 30 days from randomisation.

Funding sources

Four studies reported the funding sources for the trial (Grossman 1980; Murphy 1982; Stanworth 2013; Wandt 2012). All sources of funding were either from charitable foundations or government funds.

Ongoing studies

This review identified one ongoing study that was eligible for inclusion, the [NCT01615146](#). The [NCT01615146](#) is a feasibility study in adults with myelodysplastic syndrome and severe thrombocytopenia receiving outpatient supportive therapy. The study was due for completion in June 2014, however the study was put on hold due to poor study accrual. Study authors are expected to present their findings later this year.

The previous systematic review, [Estcourt 2012a](#), identified five potentially relevant trials; three of these have since been excluded because they were studying the wrong intervention ([Franklin 1995](#); [Lu 2011](#); [NCT00180986](#)), and two are now included in this systematic review ([Stanworth 2013](#); [Wandt 2012](#)).

See [Characteristics of ongoing studies](#) for further details.

Excluded studies

See [Characteristics of excluded studies](#) for further details.

- Twelve studies compared different participant groups: [Andrew 1993](#); [Arnold 2006](#); [Bai 2004](#); [Fanning 1995](#); [Gajic 2006](#); [Gerday 2009](#); [Johansson 2007](#); [Julmy 2009](#); [NCT00699621](#); [Reed 1986](#); [Speiss 2004](#); [Vadhan-Raj 2002](#)
- Sixty-four 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](#); [Blundell 1996](#); [Carr 1990](#); [Couban 2002](#); [de Wildt-Eggen 2000](#); [Diedrich 2005](#); [Diedrich 2009](#); [Dumont 2011](#); [Franklin 1995](#); [Gmür 1983](#); [Goodnough 2001](#); [Goodrich 2008](#); [Gurkan 2007](#); [Harrup 1999](#); [Heal 1993](#); [Heckman 1997](#); [Heddle 1994](#); [Heddle 1999](#); [Heddle 2002](#); [Heddle 2009](#); [Higby 1974](#); [ISRCTN49080246](#); [Kakaiya 1981](#); [Kerkhoffs 2010](#); [Klumpp 1999](#); [Lapierre 2003](#); [Leach 1991](#); [Lee 1989](#); [Lozano 2010](#); [Lozano 2011](#); [Lu 2011](#); [McCullough 2004](#); [Messerschmidt 1988](#); [Mirasol 2010](#); [Murphy](#)

[1986](#); [NCT00180986](#); [Oksanen 1991](#); [Oksanen 1994](#); [Pamphilon 1996](#); [Rebulla 1997](#); [Roy 1973](#); [Schiffer 1983](#); [Sensebe 2004](#); [Shanwell 1992](#); [Singer 1988](#); [Sintnicolaas 1995](#); [Slichter 2006](#); [Slichter 2010](#); [Steffens 2002](#); [Strindberg 1996](#); [Sweeney 2000](#); [Tinmouth 2004](#); [TRAP 1997](#); [van Marwijk Kooy 1991](#); [van Rhenen 2003](#); [Wang 2002](#); [Williamson 1994](#); [Zhao 2002](#); [Zumberg 2002](#)

- Three citations were guidelines: [Follea 2004](#); [Samama 2005](#); [Tosetto 2009](#)
- One citation was an audit: [Qureshi 2007](#)
- One study had fewer than 80% of participants with a haematological disorder: [Hoque 2013](#)
- Thirty-six citations were reviews (including three systematic 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](#); [Jelic 2006](#); [Levi 2002](#); [Lordkipanidze 2009](#); [Lozano 2003](#); [Martel 2004](#); [McNicol 2003](#); [Paramo 2004](#); [Poon 2003](#); [Rabinowitz 2010](#); [Rayment 2005](#); [Roberts 2003](#); [Sakakura 2003](#); [Shehata 2009](#); [Shen 2007](#); [Slichter 2004](#); [Slichter 2007](#); [Sosa 2003](#); [Strauss 2004](#); [Strauss 2005](#); [Tinmouth 2003](#); [Wandt 2010](#); [Wang 2005](#); [Woodard 2002](#); [Zeller 2014](#)
- Twenty-five studies were not RCTs: [Aderka 1986](#); [Callow 2002](#); [Cameron 2007](#); [Chaoui 2005](#); [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](#)

Risk of bias in included studies

None of the included studies were at low risk of bias in every domain, and all of the studies identified had some threats to validity. Only one study was deemed to be at low risk of bias in all domains other than blinding.

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

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

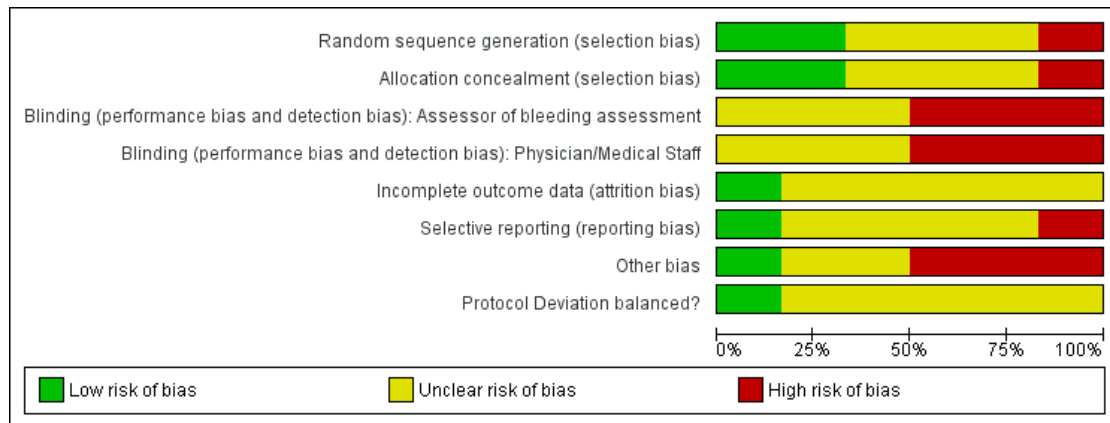


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Assessor of bleeding assessment	Blinding (performance bias and detection bias): Physician/Medical Staff	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Protocol Deviation balanced?
Grossman 1980	⊖	⊖	⊖	⊖	?	?	?	?
Murphy 1982	?	?	?	?	?	⊖	⊖	?
Sintnicolaas 1982	?	?	?	?	?	?	⊖	?
Solomon 1978	?	?	?	?	?	?	⊖	?
Stanworth 2013	⊕	⊕	⊖	⊖	⊕	⊕	⊕	⊕
Wandt 2012	⊕	⊕	⊖	⊖	?	?	?	?

The four studies published in the 1970s and 1980s had significant threats to validity; the majority of these potential risks were due to a lack of detail provided on the specific criteria and were thus judged as at unclear risk of bias (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Solomon 1978).

Allocation

Three studies reported on sequence generation and allocation concealment (Grossman 1980; Stanworth 2013; Wandt 2012). We deemed two of these studies as at low risk of selection bias (Stanworth 2013; Wandt 2012). In the third study, Grossman 1980, we deemed the method of randomisation as at high risk of selection bias because the method of random sequence generation and allocation concealment performed (unpublished data reported by the author) meant study investigators could potentially predict the study group assignment. Randomisation was performed using 25 envelopes, each with four cards inside: 1) therapeutic/random donor, 2) therapeutic/single donor, 3) prophylactic/random donor, and 4) prophylactic/single donor. Participants' allocation was drawn from the envelope as they enrolled. Once all four cards in an envelope were used, a new envelope was opened.

The three remaining studies did not report the method of allocation concealment or randomisation and have an unclear risk of selection bias (Murphy 1982; Sintnicolaas 1982; Solomon 1978).

Blinding

All studies were at high or unclear risk of detection bias. Three studies reported that they were unblinded and were therefore judged as at high risk of detection bias (Grossman 1980; Stanworth 2013; Wandt 2012). Three studies did not report any mechanisms to blind outcome assessors, clinicians, or study participants to the intervention (Murphy 1982; Sintnicolaas 1982; Solomon 1978). It is likely these studies were unblinded, owing to the nature of the intervention and difficulty blinding clinicians and participants to transfusion intervention status. It is likely that clinicians and participants were aware of study group assignment and treatment. This may have been particularly problematic with respect to reporting outcomes with potentially high levels of subjectivity, such as enumerating significant bleeding events and participant reporting of bleeding events. Studies in which the bleeding assessor was also the person deciding whether a therapeutic platelet transfusion was appropriate were at the highest risk of this type of bias.

Incomplete outcome data

Only one study, Stanworth 2013, reported completeness of data and how missing data were dealt with, and we deemed this study as at low risk of attrition bias. In the rest of the studies there was insufficient reporting to allow assessment of whether data collec-

tion was complete, and we therefore deemed them as at unclear risk of attrition bias.

The number of participants lost to follow-up was quite low in all studies.

Three studies reported using intention-to-treat analysis (Grossman 1980; Stanworth 2013; Wandt 2012). In Solomon 1978, analysis was not by intention-to-treat, as two participants (randomised to the prophylactic arm) died from cerebral haemorrhages on day one of the study and were excluded from the analysis.

Selective reporting

Study protocols or clinical trials registration information were only available for two of the six studies (Stanworth 2013; Wandt 2012). Stanworth 2013 reported on all prespecified outcomes and was at low risk of reporting bias. Wandt 2012 did not report a prespecified secondary outcome, "duration of thrombocytopenia below 10.000/ μ L", however they did report "duration of thrombocytopenia below 20.000/ μ L"; the implications of this are unclear. It was unclear whether any of the older studies were free of selective reporting, as study protocols were not available. Grossman 1980 reported on red cell and white cell transfusion in the abstract, however this was excluded from the final manuscript; whether these were prespecified outcomes within the study was unclear.

Murphy 1982 reported in the text that there was "no correlation of the incidence of bleeding with sex, pre-transfusion haematocrit, concomitant corticosteroid therapy or the use of specific antineoplastic drugs", however none of these measures were reported further.

Protocol deviation

Three of the six studies reported protocol deviation (Grossman 1980; Stanworth 2013; Wandt 2012). There were low levels of protocol deviation in Stanworth 2013, and we therefore categorised this as at low risk of bias. Slight variation in protocol deviation between the treatment arms was noted in Grossman 1980 and Wandt 2012, however the significance of this was unclear.

Other potential sources of bias

Only one study was at low risk of other biases (Stanworth 2013). Although this was a multinational study and therefore at risk of variability in the assessment of bleeding, this was mitigated by a training and monitoring policy the study set up (see Characteristics of included studies). Multicentre studies are at risk of potential heterogeneity of reporting of outcomes at different sites.

Three of the six studies were small (12 to 56 participants enrolled) (Murphy 1982; Sintnicolaas 1982; Solomon 1978). The small

number of participants in these studies reduced the likelihood that participants were equivalent at baseline. Two studies did not have equivalent numbers of participants in each study arm at baseline (Murphy 1982; Solomon 1978), and Sintnicolaas 1982 did not report the number of participants in each study arm. We judged these three studies as at high risk of 'other bias'.

Two studies reported interim data from the study prior to the study's completion (Grossman 1980; Wandt 2012). These interim results may have affected the behaviour of clinicians involved in these studies, including recruitment of participants, assessment and reporting of bleeding, and change in platelet prescription practice.

Risk of bias in the assessment and grading of bleeding

All methods of bleeding assessment are prone to performance and detection bias because it is a subjective measurement.

Four of the six studies reported bleeding outcomes (Grossman 1980; Murphy 1982; Stanworth 2013; Wandt 2012). Bleeding was the primary outcome measure in one of these studies (Stanworth 2013).

Three studies reported the method used to assess for the presence of bleeding (Grossman 1980; Stanworth 2013; Wandt 2012) (Table 2).

In Grossman 1980, participants were assessed daily for signs of bleeding and fundoscopic examination was performed twice daily once the platelet count was less than $20 \times 10^9/L$. In Stanworth 2013, an unblinded local research nurse performed daily bleeding assessments, or participants self reported bleeding in a bleeding diary. In Wandt 2012, experienced medical staff performed twice-daily bleeding assessments.

Three studies reported a bleeding severity scale (Grossman 1980; Stanworth 2013; Wandt 2012). Both Stanworth 2013 and Wandt 2012 used their own modifications of the WHO grading scale and defined clinically relevant bleeding as bleeding of WHO Grade 2 or higher. Grossman 1980 classified bleeds as mild or severe; mild bleeds were those that did not require active intervention.

Two studies reported how an assessment of bleeding was converted into a bleeding grade (Stanworth 2013; Wandt 2012). In Stanworth 2013, a validated computer algorithm performed grading of bleeding. In Wandt 2012, two investigators masked to treatment strategy transformed the bedside report into modified WHO categories.

One of the main definitions for WHO Grade 3 bleeding, in the modified WHO criteria is bleeding necessitating red cell transfusion support. Four studies reported red cell transfusion requirements (Grossman 1980; Solomon 1978; Stanworth 2013; Wandt 2012), however only two studies described their red cell transfusion policy (Stanworth 2013; Wandt 2012). The red cell transfusion policy differed between studies, and this variance could potentially affect the assessment of bleeding grade and lead to bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation

In all the included studies, we used the study's own definition of clinically significant bleeding, unless otherwise stated. If the study did not explicitly define clinically significant bleeding, we assumed that this was WHO Grade 2 or above bleeding. The two more recent studies used their own modifications of the WHO grading scale (Stanworth 2013; Wandt 2012). Grossman 1980 defined mild bleeds as bleeds not needing active intervention, with no specific definition given for "severe" bleeds.

Primary outcome

Four of the six studies reported bleeding as an outcome measure (Grossman 1980; Murphy 1982; Stanworth 2013; Wandt 2012). (See Table 3, Table 4, Table 5 for individual study results.) The duration of follow-up varied between studies. In Stanworth 2013, the median number of days on study was 30 days. Grossman 1980 followed up participants throughout their initial hospital stay and all subsequent admissions. Days on study was defined as a platelet count less than $50 \times 10^9/L$, and the mean length of follow-up was 41.6 days in the therapeutic-only group and 42.7 days in the prophylactic group.

Wandt 2012 followed participants until either the platelet count was self sustaining at $20 \times 10^9/L$ or higher for two days; a maximum of 30 days; at hospital discharge; when treatment failure occurred; at death or at study withdrawal, whichever occurred first. Wandt 2012 reported bleeding events per treatment cycle. In the autologous HSCT group, the number of participants was equal to the number of treatment cycles, and therefore each participant received only one treatment cycle. Participants with AML had bleeding events reported per treatment cycles received, therefore the number of participants did not equal the number of treatment cycles. Consequently we were unable to include this data for the AML group in the meta-analysis.

Murphy 1982 followed up participants from study enrolment until study closure. Bleeding outcomes and platelet transfusion requirements were reported for the first 10 months of the study and until study closure. The mean number of months observed varied from 20.4 months in the therapeutic-only group to 19.9 months in the prophylactic group.

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

Two of the six studies reported bleeding outcomes within 30 days from the start of the study (Stanworth 2013; Wandt 2012).

Number of participants with at least one bleeding episode

Two studies reported the number of participants with a clinically significant bleeding event (Stanworth 2013; Wandt 2012 (autologous HSCT participant data only)). We did not perform a meta-analysis of the data from these two studies due to the significant statistical heterogeneity seen ($I^2 = 88\%$) (Stanworth 2013; Wandt 2012). We identified a probable cause for this heterogeneity, that is the different ways in which these two trials assessed and recorded bleeding (Characteristics of included studies). These results are represented graphically in Analysis 1.1. In Stanworth 2013, there appeared to be an increased risk of bleeding events with a therapeutic-only transfusion policy when compared with the prophylactic group; however, the 95% confidence interval (CI) crossed 1.0 (risk ratio (RR) 1.17, 95% CI 0.99 to 1.39). In Wandt 2012, a therapeutic-only transfusion policy was associated with increased risk of bleeding events per treatment cycle when compared with a prophylaxis policy (RR 3.45, 95% CI 1.66 to 7.17).

Two studies did not report bleeding events over 30 days and therefore could not be included in the meta-analysis, as they had varying definitions of study completion and reported clinically significant bleeding episodes over different time periods (Grossman 1980; Murphy 1982). We sought additional data from study authors to enable us to perform meta-analysis of bleeding outcomes, however individual bleeding data for the first 30 days postrandomisation were not available from Grossman 1980, and the study author from Murphy 1982 died prior to publication of this review. These studies both reported a similar effect with statistically increased clinically significant bleeding in the therapeutic-only platelet transfusion group when compared with the prophylactic arm (see Table 3).

Wandt 2012 reported bleeding using different units of analysis, and we were therefore unable to incorporate the data from the participants with AML in the meta-analysis; further individual bleeding data per participant is pending. On review of the combined results in Wandt 2012 (see Table 3), the study showed a statistically increased risk of bleeding events with a therapeutic-only platelet transfusion policy when compared with a prophylactic platelet regimen.

Total number of days on which bleeding occurred per participant

Two of the six studies reported the number of days with a significant bleeding event per participant (Murphy 1982; Stanworth 2013) (see Table 4). However, only one of the studies, Stanworth 2013, reported the total number of days within 30 days from the start of the study. Murphy 1982 did not report this outcome over 30 days and was therefore not included in the meta-analysis.

In Stanworth 2013, the number of days with clinically significant bleeding per participant was higher in the therapeutic-only group than in the prophylactic group (mean difference (MD) 0.50, 95% CI 0.10 to 0.90) (Analysis 1.2).

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

Three studies reported the number of participants with at least one episode of severe or life-threatening bleeding (Grossman 1980; Stanworth 2013; Wandt 2012) (see Table 5). However, only two of the studies reported this within 30 days from the start of the study (Stanworth 2013; Wandt 2012). We were able to include the data from two studies in the meta-analysis (Stanworth 2013; Wandt 2012 (autologous HSCT participant data only)). There was no evidence of a difference in the number of participants experiencing severe or life-threatening bleeding between a therapeutic-only or prophylactic platelet transfusion policy (RR 4.91, 95% CI 0.86 to 28.12), however the 95% CI was very wide. There was no evidence of statistical heterogeneity (Analysis 1.3).

Time to first bleeding episode from the start of the study

Three studies reported the time to the first significant bleeding event (Murphy 1982; Stanworth 2013; Wandt 2012). Wandt 2012 reported graphically the time to onset of first bleeding episode. We extracted the data from the graph in Wandt 2012 using the methodology outlined by Tierney 2007. Murphy 1982 also reported graphically the percentage of participants free of bleeding at intervals following randomisation over the entire trial period. We were unable to extract data from the graph in Murphy 1982 as it was not possible to derive the timing of the first data point. We did not perform a meta-analysis of the data from Stanworth 2013 and Wandt 2012 because of the significant statistical heterogeneity seen ($I^2 = 90\%$). The individual study results have been presented graphically (Analysis 1.4). We identified a probable cause for this heterogeneity, that is the different ways in which these two trials assessed and recorded bleeding (Characteristics of included studies). In Stanworth 2013, the time to onset of significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (hazard ratio (HR) 1.30, 95% CI 1.03 to 1.64). In Wandt 2012, the time to onset of significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (HR 2.61, 95% CI 1.84 to 3.72).

Murphy 1982 reported from their analysis that the time to onset of clinically significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (study authors reported a P value of 0.014).

Secondary outcomes

Mortality within 30 and 90 days from the start of the study

Four of the six studies reported all-cause mortality as an outcome (Murphy 1982; Solomon 1978; Stanworth 2013; Wandt 2012). All six studies reported mortality due to bleeding as an outcome (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Solomon

1978; Stanworth 2013; Wandt 2012). The duration of follow-up varied widely between studies, and the definition of study completion also varied between studies, hence we could not perform pooling of these studies (see Table 6).

All-cause mortality

Two of the six studies reported all-cause mortality within 30 days from the start of the study (Solomon 1978; Stanworth 2013).

Only one of these two studies reported any deaths in either study arm (Stanworth 2013) (Analysis 1.5), and this study showed no evidence of a difference in mortality between the therapeutic-only and prophylactic platelet transfusion groups (RR 1.24, 95% CI 0.34 to 4.58).

None of the studies reported all-cause mortality within 90 days from the start of the study.

Mortality secondary to bleeding

Four of the six studies reported mortality secondary to bleeding within 30 days from the start of the study (Sintnicolaas 1982; Solomon 1978; Stanworth 2013; Wandt 2012 (autologous HSCT participants only)). None of these studies reported any secondary deaths due to bleeding (see Table 6).

Two of the six studies reported mortality secondary to bleeding within 90 days from the start of the study (Grossman 1980; Wandt 2012 (autologous HSCT participants only)) (see Table 6). We were unable to perform a meta-analysis because only one of the studies reported any deaths due to bleeding (Grossman 1980) (Analysis 1.6). This study showed no statistical difference in mortality due to bleeding between a therapeutic-only platelet transfusion policy and prophylactic platelet transfusions (RR 2.40, 95% CI 0.81 to 7.15).

Mortality secondary to infection

Only one of the six studies reported mortality secondary to infection within 30 days from the start of the study (Stanworth 2013) (see Table 6). There were 4/301 deaths in the therapeutic-only platelet transfusion group compared with 3/299 deaths in the prophylactic platelet transfusion group. All deaths secondary to infection were categorised as being unlikely to be related to the study intervention.

None of the studies reported mortality due to infection within 90 days from the start of the study.

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

Four out of the six studies reported the number of platelet transfusions given per participant (Grossman 1980; Murphy 1982; Stanworth 2013; Wandt 2012) (see Table 7). However, only two

of these four studies reported the number of platelet transfusions given within 30 days from the start of the study (Stanworth 2013; Wandt 2012).

Wandt 2012's primary outcome was number of platelet transfusions given during a standardised observation time of 14 days per participant. The observation time was standardised to fairly compare the number of platelet transfusions between the two transfusions groups despite a different duration of observation in participants who underwent differing numbers of treatment cycles. We therefore included this data in the meta-analysis. Both of these studies reported a clear reduction in the number of platelet transfusions per participant. The meta-analysis showed a standardised mean reduction of 0.50 platelet transfusions per participant (95% CI -0.63 to -0.37) (Analysis 1.7).

Three out of the six studies reported the number of platelet components given per participant (Murphy 1982; Solomon 1978; Stanworth 2013) (see Table 7).

Only one study reported the number of platelet components per participant within 30 days from the start of the study (Stanworth 2013). There was a mean reduction of 1.30 platelet units per participant (95% CI -1.85 to -0.75) (see Table 7).

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

Four out of the six studies reported red cell transfusion requirements as an outcome (Grossman 1980; Solomon 1978; Stanworth 2013; Wandt 2012) (see Table 8). Two of the six studies reported the number of red cell transfusions per participant within 30 days of the study (Stanworth 2013; Wandt 2012 (autologous HSCT participants only)). The meta-analysis showed there was no evidence of a difference in red cell transfusions per participant (MD 0.11, 95% CI -0.14 to 0.36) (Analysis 1.8). There was a moderate degree of heterogeneity seen between studies ($I^2 = 65\%$), and this may reflect differences in red cell transfusion policies.

Two out of the six studies reported number of red cell components per participant as an outcome (Solomon 1978; Stanworth 2013) (see Table 8).

Only one study, Stanworth 2013, reported the mean number of red cell components per participant within 30 days from the start of the study (MD 0.20, 95% CI -0.32 to 0.72) (see Table 8).

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

None of the six studies reported the platelet transfusion interval.

Proportion of participants requiring additional interventions to stop bleeding within 30 days from the start of the study

Two studies provided unpublished data on the use of blood product and surgical interventions to stop WHO Grade 3 and 4 bleeding (Stanworth 2013; Wandt 2012).

Additional surgical interventions to stop bleeding

Both Stanworth 2013 and Wandt 2012 (unpublished data) reported the use of surgical, endoscopic, or other procedures to stop bleeding. There was no evidence of a difference in the use of surgical or other procedures (RR 3.96, 95% CI 0.44 to 35.27) (Analysis 1.9).

Additional medical interventions to stop bleeding

Stanworth 2013 (unpublished data) reported the use of medical interventions to stop bleeding. There was no evidence of a difference in the use of medical interventions to stop bleeding between the therapeutic-only platelet transfusion arm and the prophylactic arm (RR 4.97, 95% CI 0.24 to 103.02) (Analysis 1.10). The number of events was low, and the 95% CI was very wide. Interventions Stanworth 2013 reported included tranexamic acid and vitamin K.

Additional blood product interventions to stop bleeding

Two of the six studies reported the use of blood product interventions to stop WHO Grade 3 and 4 bleeding (Stanworth 2013; Wandt 2012) (unpublished data), and no studies reported the use of blood products to stop WHO Grade 2 bleeding. There was no evidence of a difference in the use of blood products to stop WHO Grade 3 or 4 bleeding between the therapeutic-only platelet transfusion arm and the prophylactic arm (RR 0.71, 95% CI 0.14 to 3.55) (Analysis 1.11).

Blood products used to stop bleeding included fresh frozen plasma, clotting factor concentrate, and factor XIII. There were no reports of the use of cryoprecipitate, fibrinogen, or recombinant factor VIIa to stop bleeding.

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

Three of the six studies reported overall survival (Murphy 1982; Stanworth 2013; Wandt 2012). However, only one study reported overall survival rate at 30 days: 297/301 in the therapeutic-only group and 297/299 in the prophylactic group (Stanworth 2013). None of the studies reported overall survival within 90 or 180 days from the start of the study.

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

Only one of the six studies reported complete or partial remission rates (Solomon 1978). The study reported complete remission rates after one course of chemotherapy. Those who did not achieve complete remission were generally given a second course

of chemotherapy. Complete remission was achieved in 9/17 from the prophylactic platelet transfusion group and 6/12 in the specific interventions group (therapeutic-only platelet transfusions and platelet transfusions when there was a 50% or more decline in platelet count in the preceding 24 hours) (RR 0.94, 95% CI 0.46 to 1.94) (Analysis 1.12).

None of the studies reported complete remission rates at 30 or 90 days.

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

Two of the six studies reported the total time of hospitalisation (Stanworth 2013; Wandt 2012). However, the studies reported this data in different formats, and therefore we could not combine them in a meta-analysis. Stanworth 2013 reported a median duration of inpatient stay per participant of 12 days (interquartile range (IQR) 9 to 18) in the therapeutic-only group and 12 days (IQR 9 to 18) in the prophylactic group. Wandt 2012 reported mean number of days in hospital: 18 days (95% CI 17 to 18) in the therapeutic-only group, compared with 17 days (95% CI 16 to 19) in the prophylactic group; the study's reported P value was 0.69. There was no evidence of a difference in the total time in hospital between the two intervention groups in these two studies.

Adverse effects of treatments within 30 and 90 days from the start of the study

Five of the six studies reported adverse effects of transfusion (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Stanworth 2013; Wandt 2012).

Transfusion reactions

Two of the five studies reported the occurrence of transfusion reactions within 30 days from the start of the study (Stanworth 2013; Wandt 2012). We performed a meta-analysis of data from these two studies and observed no evidence of a difference in the number of transfusion reactions between a therapeutic-only or prophylactic platelet transfusion policy (RR 1.02, 95% CI 0.62 to 1.68). There was no evidence of heterogeneity (Analysis 1.13). There was considerable difference in the rates of reported transfusion reactions between these studies. This may be a reflection of variability between the studies in how transfusion reactions were defined, identified, and reported.

Thromboembolic disease

None of the studies reported the occurrence of thromboembolic disease.

Transfusion-transmitted infection

None of the studies reported the occurrence of transfusion-transmitted infection.

Human leukocyte antigen antibodies/platelet refractoriness

Three of the five studies reported platelet refractoriness as an outcome (Grossman 1980; Murphy 1982; Sintnicolaas 1982) (see Table 9). Two of the studies defined platelet refractoriness (Grossman 1980; Murphy 1982). Murphy 1982 defined it as bleeding for more than four days, in which thrombocytopenia persists in the face of repeated platelet transfusions. Grossman 1980 defined platelet refractoriness as a corrected count increment of less than $10 \times 10^9/L$ following two or more consecutive transfusions in the absence of fever, disseminated intravascular coagulopathy, splenomegaly, or sepsis.

No studies reported platelet refractoriness within 30 days of the start of the study (see Table 9).

Quality of life, as defined by the individual studies

None of the six studies reported any quality-of-life outcomes.

Prespecified subgroup analyses

See Table 10.

Presence of fever

None of the studies commented on an association between fever and bleeding risk.

Underlying disease

Three studies reported bleeding outcome data on the basis of the participants' underlying haematological disease (Murphy 1982; Stanworth 2013; Wandt 2012) (Stanworth 2013 also provided unpublished data) (Analysis 1.14).

Wandt 2012 reported separate subgroup data for participants with AML and autologous HSCT. The data for the participants being treated for AML and autologous HSCT were reported per treatment cycle rather than per participant, and hence participants with AML may have received more than one treatment cycle, with the consequence that we were unable to include the data in the meta-analysis.

The AML subgroup from Wandt 2012 had increased bleeding rates in the therapeutic-only platelet transfusion group. There were 98 bleeding episodes per 198 treatment cycles with a therapeutic-only regimen compared with 57 bleeding episodes per 245 treatment cycles in participants receiving a prophylactic platelet transfusion (study authors reported a P value of less than 0.0001).

Murphy 1982 did not report the outcome within 30 days.

Number of participants with at least one clinically significant bleeding episode

Stanworth 2013 reported bleeding outcome data on the basis of the participants' underlying haematological disease for three subgroups: acute leukaemia, lymphoma/myeloma, and chronic myelogenous leukaemia (CML)/other cancer within 30 days from the start of the study.

Analysis of the data from Stanworth 2013 for participants with acute leukaemia showed there was an increase in the number of participants developing clinically significant bleeding with a therapeutic-only transfusion policy when compared with a prophylactic policy (RR 1.64, 95% CI 1.11 to 2.44) (Analysis 1.14).

Subgroup analysis from Stanworth 2013 for participants with lymphoma/myeloma showed no evidence of a difference in bleeding events between the intervention groups (RR 1.07, 95% CI 0.88 to 1.31). Similarly, there was no evidence of a difference in bleeding rates for participants with CML or other cancer (RR 1.07, 95% CI 0.50 to 2.28) (Analysis 1.14).

Type of treatment

Two trials reported bleeding outcome data separately for participants receiving autologous HSCT (Stanworth 2013; Wandt 2012). Stanworth 2013 (unpublished data) also reported bleeding outcomes for participants receiving chemotherapy/allogeneic HSCT.

Number of participants with at least one clinically significant bleeding episode

We did not perform a meta-analysis of the data for participants receiving autologous HSCT as there was considerable statistical heterogeneity between these two studies: $I^2 = 90\%$ (Analysis 1.15). This statistical heterogeneity may have arisen because of the known differences in how bleeding was assessed and graded, the difference in autologous stem cell protocols and source of stem cells used for the transplantation. There was variability in the baseline participant characteristics between the two studies, specifically with regard to underlying haematological disease requiring HSCT. In Stanworth 2013, no participants received autologous HSCT for acute leukaemia, whilst in Wandt 2012, 14 participants were transplanted for acute leukaemia.

In Stanworth 2013, there was no evidence of a difference in the number of clinically significant bleeding episodes between a therapeutic-only or prophylactic platelet transfusion policy (RR 1.04, 95% CI 0.85 to 1.28). However, in Wandt 2012 there was a difference (RR 3.45, 95% CI 1.66 to 7.17) (Analysis 1.15).

In Stanworth 2013 (unpublished data), there was a difference in the number of clinically significant bleeding episodes between a therapeutic-only and prophylactic platelet transfusion policy in the chemotherapy group (RR 1.55, 95% CI 1.05 to 2.28) (Analysis

1.15). There was no evidence of a difference in bleeding between intervention groups in the allogeneic HSCT group in [Stanworth 2013](#) (RR 1.50, 95% CI 0.86 to 2.61) ([Analysis 1.15](#)).

Total number of days in which bleeding occurred per participant

The number of days with a significant bleeding event per participant was reported in [Stanworth 2013](#) for the autologous HSCT and chemotherapy/allogeneic HSCT groups [Stanworth 2013](#) (unpublished data). In the autologous HSCT group, there was no difference in the number of days with clinically significant bleeding per participant between the therapeutic-only platelet transfusion group and the prophylactic group (MD 0.30, 95% CI -0.07 to 0.67) ([Analysis 1.16](#)).

In the chemotherapy/allogeneic HSCT group (unpublished data), the number of days with clinically significant bleeding per participant was higher in the therapeutic-only group than in the prophylactic platelet transfusion group (MD 1.20, 95% CI 0.22 to 2.18) ([Analysis 1.16](#)).

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

[Stanworth 2013](#) and [Wandt 2012](#) reported the number of participants with at least one episode of severe or life-threatening bleeding for participants receiving autologous HSCT. [Stanworth 2013](#) (unpublished data) also reported severe or life-threatening bleeding in the chemotherapy/allogeneic HSCT group.

In the autologous HSCT group, there was no evidence of a difference in the number of participants experiencing severe or life-threatening bleeding between a therapeutic-only or prophylactic platelet transfusion policy (RR 4.89, 95% CI 0.58 to 41.41) ([Analysis 1.17](#)); however, the 95% CI was very wide.

In the chemotherapy/allogeneic HSCT group from [Stanworth 2013](#) (unpublished data), there was no evidence of a difference in the number of participants experiencing severe or life-threatening bleeding between a therapeutic-only or prophylactic platelet transfusion policy (RR 2.97, 95% CI 0.31 to 27.98) ([Analysis 1.18](#)).

Time to first bleeding episode from the start of the study

[Stanworth 2013](#) reported the time to first bleeding episode from the start of the study for the autologous HSCT and chemotherapy/allogeneic HSCT groups (unpublished data). In the autologous HSCT group, there was no evidence of a difference in the time to onset of significant bleeding between the therapeutic-only group and prophylaxis group (MD -0.70, 95% CI -3.16 to 1.76) ([Analysis 1.19](#)).

In the chemotherapy/allogeneic HSCT group ([Stanworth 2013](#) unpublished data), the time to onset of significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (MD -6.00, 95% CI -9.52 to -2.48) ([Analysis 1.19](#)).

Age of participant

One study, [Stanworth 2013](#), provided unpublished data looking at the number of participants with at least one bleeding episode in participants aged 18 to less than 60 years and participants aged 60 years or older. In participants aged 18 to less than 60 years, there was no evidence of a difference in bleeding rates between the treatment groups (RR 1.15, 95% CI 0.90 to 1.47). Similarly, in participants aged 60 years or older, there was no evidence of a difference in bleeding rates seen (RR 1.19, 95% CI 0.93 to 1.51) ([Analysis 1.20](#)).

DISCUSSION

Summary of main results

This Cochrane systematic review intended to evaluate whether a therapeutic-only platelet transfusion policy (platelet transfusions given when a patient bleeds) is as effective and safe as a prophylactic platelet transfusion policy (platelet transfusions given to prevent bleeding, usually when the platelet count falls below a given threshold) in people with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation.

We identified seven RCTs that met our inclusion criteria, one of which is currently recruiting participants ([NCT01615146](#)). We included six trials that compared the effect of a therapeutic-only versus prophylactic platelet transfusion policy in the review. These trials were carried out over a 35-year period and enrolled 1195 participants from fairly comparable patient populations. Five of these studies contained separate data for each arm and could therefore be critically appraised.

Clinically significant bleeding events

One of the main challenges within this review was the variability between studies in the assessment and grading of bleeding, the time period for which bleeding was reported across, and the units of analysis. The two recent studies used their own modifications of the WHO classification scale ([Stanworth 2013](#); [Wandt 2012](#)). WHO Grade 3 bleeding was defined as bleeding requiring red cell transfusions, however the red cell transfusion policies varied between studies. The method in which bleeding was recorded varied between studies and hampered the incorporation of study data into the meta-analysis. [Wandt 2012](#) recorded bleeding in participants with AML per treatment cycle, and we were therefore

unable to include it in the meta-analysis. The time period for which bleeding was reported across was not consistent between trials.

For the primary outcome (number of participants with at least one bleeding episode within 30 days from the start of the study), we observed significant statistical heterogeneity between studies, and were therefore unable to perform a meta-analysis. This statistical heterogeneity may relate to the different methods the studies used to assess and grade bleeding and the different participant populations, in particular underlying disease and treatment categories.

Whilst we were unable to perform a meta-analysis for clinically significant bleeding events, all studies individually showed a similar effect. When compared with a prophylactic platelet transfusion policy, a therapeutic-only platelet transfusion policy was associated with increased rates of clinically significant bleeding events.

One study reported the number of days with a clinically significant bleeding event per participant, and this was statistically higher in the therapeutic-only group than in the prophylactic group.

There was insufficient evidence to determine whether there was any difference in the number of participants with severe or life-threatening bleeding between a therapeutic-only transfusion policy and a prophylactic policy. The numbers of episodes of severe and life-threatening bleeding were small, and whilst we saw no statistical difference between treatment interventions, the confidence intervals were wide. Larger studies would be needed to detect any difference in life-threatening bleeding rates.

The time to first bleeding event appeared shorter in participants receiving a therapeutic-only platelet transfusion policy versus a prophylactic platelet transfusion policy.

Rates of bleeding appeared to differ amongst different participant disease-type and treatment groups.

We were unable to perform a meta-analysis for bleeding rates in participants with acute leukaemia. However, two studies individually reported a statistically increased rate of bleeding in participants with acute leukaemia being managed with a therapeutic-only platelet transfusion policy versus a prophylactic policy.

One study reported rates of bleeding for participants with lymphoma/myeloma and CML/other haematological malignancies and found similar rates of bleeding in both therapeutic-only and prophylactic transfusion arms (Stanworth 2013). Further evidence is needed to confirm or refute these findings.

There was inconclusive evidence in participants receiving autologous HSCT as to whether a therapeutic-only platelet transfusion policy was associated with increased rates of clinically significant bleeding. There was significant heterogeneity between studies, and one study had wide 95% CIs. This statistical heterogeneity may have arisen because of the known differences in the way that bleeding was assessed, but may also be due to the different indications for HSCT, differences in the conditioning regimens, stem cell protocols, and the source of stem cells used for transplantation.

Adopting a therapeutic-only platelet transfusion policy would significantly reduce the number of platelet transfusions needed, how-

ever we did not assess the cost-effectiveness of introducing such a policy.

Mortality

There was insufficient evidence to determine any difference in all-cause mortality within 30 days of the start of the study between participants receiving a therapeutic-only versus a prophylactic platelet transfusion policy. The results of the individual studies suggested that there was no difference in all-cause mortality between the two intervention groups. However, due to the low mortality rates within the included studies, larger studies would be required to detect a statistical difference. There was insufficient evidence to determine whether there was any effect of a therapeutic-only platelet transfusion policy on mortality rates due to bleeding.

There was insufficient evidence to determine if there was any difference in overall survival rates at 30 days between treatment arms.

Adverse events

There was no evidence of any difference in the frequency of adverse events such as transfusion reactions between a therapeutic-only platelet transfusion policy and prophylactic platelet transfusion policy. These findings should be taken in the context that there was a large difference in the rates of reported transfusion reactions between the included studies suggesting that there was variability between how studies defined, identified, and reported transfusion reactions.

Transfusions

There was a clear reduction in the number of participants receiving platelet transfusions in the therapeutic-only platelet transfusion arm when compared with the prophylactic platelet transfusion arm.

There was no evidence of a difference in red cell transfusions between treatment groups.

Quality of life

None of the studies reported quality of life.

Overall, a therapeutic-only platelet transfusion policy did not appear as safe and effective as a prophylactic platelet transfusion policy with regard to rates of clinically significant bleeding.

In summary, the findings of the review led to the following main conclusions:

- An increased proportion of participants bled with a therapeutic-only platelet transfusion policy.
- The number of days with clinically significant bleeding increased with a therapeutic-only platelet transfusion policy.
- There was insufficient evidence to determine any difference in severe or life-threatening bleeding.

- Time to first bleeding episode was shorter in the therapeutic-only platelet transfusion group than in the prophylactic platelet transfusion group.
- There was insufficient evidence to determine any difference in all-cause mortality.
- There was a clear reduction in the number of platelet transfusions per participant in the therapeutic-only arm.
- No study reported quality of life.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of a therapeutic-only platelet transfusion policy compared with administering prophylactic platelet transfusions when the platelet count goes below a certain threshold. This review identified two recently completed RCTs and a trial from the 1980s that had not been reviewed previously.

There is evidence that haematology patients receiving myelosuppressive chemotherapy or HSCT had increased clinically significant bleeding events with a therapeutic-only platelet transfusion policy when compared with a prophylactic platelet transfusion policy. A prophylactic platelet transfusion policy appeared safer and should be continued as standard of care.

The results of this meta-analysis should not be interpreted without considering the impact of the following factors:

- The studies included in this review range over a 35-year period (1978 to 2013), during which chemotherapy protocols, predicted overall survival rates, and supportive care, including transfusion, have changed substantially.
- The recording of bleeding is subjective, and between centres there is variability in the assessment, grading, investigation, and recording of bleeding. The same bleeding scale may even be interpreted and applied differently, particularly with respect to red cell transfusion.
- A number of studies showed a similar effect, that is increased clinically significant bleeding in the therapeutic-only platelet transfusion group when compared with the prophylactic platelet transfusion group (Grossman 1980; Murphy 1982; Stanworth 2013; Wandt 2012). We could not integrate the results from the individual studies into a meta-analysis because the studies reported bleeding outcomes over different time periods, had varying definitions of study completion, or used different units of analysis.
- We could not analyse all endpoints from all the studies for this review due to varying methods of reporting bleeding. One of the larger studies conducted, Wandt 2012, reported bleeding outcomes for the AML subgroup per treatment cycle, and could not be included in the meta-analysis for bleeding events.
- Our prespecified time frames for outcome measurement resulted in the exclusion of a number of studies from meta-analysis. We could not include Grossman 1980, a medium-sized

study, for bleeding rates and mortality data due to differences in follow-up period.

- Grossman 1980 was only published in abstract form, as the full-text article was not accepted for publication.
- We were unable to obtain all data from study authors to be used quantitatively in the meta-analysis.
- Sintnicolaas 1982 did not have any usable data; the number of participants in each treatment arm was not stated, and it was therefore excluded from any quantitative analysis.
- The number of participants lost to follow-up was quite low in all studies, and there were therefore minimal implications of missing outcome data.
- Different studies used different formats for expressing results such as overall survival, and consequently could not be analysed together.
- Within the same patient subpopulation there may be significant differences between the type of chemotherapy and number of courses administered (induction chemotherapy versus consolidation therapy).
- We saw differences in the baseline characteristics of participants receiving HSCT, in particular indication for stem cell transplantation.

Quality of the evidence

All studies were RCTs, however they were all prone to bias and had threats to validity. See Figure 2 and Figure 3 for visual representations of the assessments of risk of bias across all studies and for each item in the individual studies. See Characteristics of included studies for individual information about 'Risk of bias' assessments across the trials.

The early-published studies had significant threats to validity and were at risk of selection bias due to their lack of clarity or biased study methodology including sequence generation and allocation concealment (Grossman 1980; Murphy 1982; Sintnicolaas 1982; Solomon 1978). These studies were also hampered by inadequate power due to small sample size. Study protocols were not available for these studies, and therefore it is unclear whether they were free of reporting bias.

All studies were at risk of performance and detection bias due to the nature of the intervention (platelet transfusion) and the difficulty in blinding participants and outcome assessors to the intervention group of participants. There may be a high level of subjectivity when reporting outcomes such as bleeding, particularly the assessment and classifying of bleeding events.

Those studies that published interim data results were at risk of bias. The findings of the interim analysis may have affected the behaviour of the physicians at participating sites and other centres with regard to recruitment of participants, assessment and reporting of bleeding outcomes, and prescription of platelet transfusions. Most studies were at unclear risk of attrition bias, due to insufficient information provided regarding completeness of data and

management of missing data.

Only one study was deemed to be at low risk of bias (Stanworth 2013), apart from the risk of bias due to lack of blinding.

Overall, the quality of evidence per outcome was low to moderate according to the GRADE approach.

The outcomes time to first bleeding episode and number of participants with at least one bleeding episode within 30 days from the start of the study were not estimable due to the differences in the way bleeding was assessed in the two studies.

The outcome mortality from all causes up to 30 days was not estimable, as only one of the studies reported any deaths in either study arm (Stanworth 2013).

The outcome quality of life was not estimable, as none of the six studies reported any quality-of-life outcomes.

We downgraded the estimable outcomes 'number of days with significant bleeding per participant', 'number of participants with severe or life-threatening bleeding', and 'number of platelet transfusions per participant up to 30 days from the start of the study' by one point for risk of performance and detection bias, due to the lack of blinding.

We downgraded the outcome 'number of participants with severe or life-threatening bleeding up to 30 days from the start of the study' by one point for imprecision due to the wide confidence intervals of the pooled estimates and individual trials contributing to this outcome.

Potential biases in the review process

To our knowledge, our review process is free from bias. We conducted a comprehensive search of data sources (including multiple databases and clinical trial registries) to ensure that we would capture all relevant trials. We made no restrictions for the language in which the paper was originally published. We carefully assessed the relevance of each paper identified and performed all screening and data extractions in duplicate.

We prespecified all outcomes and subgroups prior to analysis. One of the limitations of this is that we were unable to include the bleeding data and mortality rates from a number of studies because their outcomes were reported over different time frames.

The number of included trials was insufficient for us to complete a funnel plot to examine the risk of publication bias.

One potential bias in our review was that we prespecified in the protocol that we would not perform meta-analysis if there was considerable statistical heterogeneity (I^2 above 80%). This resulted in us being unable to perform a meta-analysis for our primary outcome. We identified a valid reason for this statistical heterogeneity, and therefore not performing a meta-analysis was in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

One of the authors of this review was a primary investigator of a study included in the systematic review. This author's involvement in the review process was in protocol development and as a content

expert; the author was not directly involved in data collection, analysis, or the 'Risk of bias' assessment.

Agreements and disagreements with other studies or reviews

Two platelet transfusion reviews were recently published in this area (Kumar 2014; Zeller 2014).

Zeller 2014 reviewed only the two most recent trials by Stanworth 2013 and Wandt 2012 and provides a descriptive analysis of these studies. The study authors' main conclusions were that patients receiving induction chemotherapy for acute leukaemia should continue to receive prophylactic platelet transfusions during their treatment, and patients undergoing autologous HSCT who are at low risk of bleeding in expert centres with careful monitoring may be candidates for therapeutic-only platelet transfusion.

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 only five studies (Murphy 1982; Sintnicolaas 1982; Solomon 1978; Stanworth 2013; Wandt 2012). The review authors performed meta-analyses when the included studies had very different durations of observation (for example for bleeding outcomes this was from 30 days in Stanworth 2013 to 20.4 months in Murphy 1982). Their 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. The associated guideline recommended that platelets should be transfused prophylactically in order to reduce the risk of spontaneous bleeding in hospitalised adult patients with therapy-induced hypoproliferative thrombocytopenia (Kaufman 2014).

Our review is more comprehensive and identifies a study not previously reviewed, Grossman 1980, as well as previously unpublished study data. We performed a detailed quality assessment of all identified studies and highlighted their weaknesses and shortcomings. We noted the high degree of heterogeneity between studies, the different units of analysis, and different time periods over which outcomes have been reported in the different studies, and concluded that it is not possible to combine the individual studies' results in a meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Due to the high levels of heterogeneity between the two largest identified trials and difficulties combining individual trials in the meta-analysis, our results should be interpreted with caution. When reviewing the results of the meta-analysis and the individual studies' results, there is evidence that a therapeutic-only platelet

transfusion policy is associated with increased risk of bleeding when compared with a prophylactic policy.

There was insufficient evidence for the outcomes of mortality, overall survival, or complete remission to determine whether there is a difference between these two transfusion strategies.

There was no evidence of any difference in adverse events between a therapeutic-only and a prophylactic platelet transfusion policy.

Implications for research

One of the main constraints in performing the meta-analysis in this review was the different time periods in which trials reported bleeding. Implications for future research include standardised consensus time periods for reporting outcomes of interest such as bleeding.

Further research is needed to identify the subgroups of patients for which it may be safe to adopt a therapeutic-only platelet transfusion policy, in particular patients receiving autologous HSCT. Whether the conditioning regimens, indication for HSCT, and number of viable CD34 positive cells in the autologous HSCT have any impact on duration of thrombocytopenia and bleeding rates. Another cohort of haematology patients who currently receive regular platelet transfusions include people with myelodysplasia, and an ongoing trial will be able to add further evidence in

this area. Other areas of interest are the differences in leukaemia patients receiving different intensities of chemotherapy, that is induction chemotherapy versus consolidation chemotherapy.

Double-blind, placebo-controlled RCTs are not feasible to compare a therapeutic-only versus prophylactic platelet transfusion policy because clinicians will be unblinded when they see the participants' platelet counts rise after receiving a prophylactic platelet transfusion and not rise after receiving a placebo. There is also a safety issue for participants. There is a risk that participants may receive placebo rather than a platelet transfusion when they have severe or life-threatening bleeding. However, blinding assessors of bleeding to the intervention is feasible if they do not see any of the participants' blood results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Grossman 1980

Methods	Factorial RCT (period of enrolment not reported). Single centre. Canada
Participants	<p>Inclusion criteria: Patients with amegakaryocytic thrombocytopenia treated at Vancouver General Hospital</p> <p>Exclusion criteria: Known to be refractory to platelet transfusions, if they were no longer candidates for aggressive therapy or if their thrombocytopenia was not expected to last for more than 7 days</p> <p>N = 100 participants randomised</p> <p>Arm 1 and 2 (therapeutic): N = 51, ANLL = 31; ALL = 8; AA = 5; Other = 7</p> <p>Arm 3 and 4 (prophylactic): N = 49, ANLL = 37; ALL = 8; AA = 1; Other = 3</p>
Interventions	<p>Comparison between therapeutic-only and prophylactic platelet transfusion. Within these two comparisons, participants were also randomised to receive SD versus BB, also referred to as RD platelet transfusions</p> <p>N = 100</p> <p>Arm 1 and 2 (Therapeutic): Platelet transfusions were given for clinically significant bleeding and just prior to invasive procedures</p> <p>Arm 3 and 4 (Prophylactic): Platelet transfusions were given to maintain platelet count above $20 \times 10^9/L$</p> <p>Reasons to change a platelet transfusion trigger:</p> <p>In the prophylactic arm, if alloimmunisation occurred, participants were transfused only for significant bleeding, and if they were receiving BB platelets, they were also switched to SD platelets</p> <p>It is unclear whether platelets were given in the prophylactic arm prior to invasive procedures and in the setting of clinically significant bleeding</p> <p>Platelet dose: A SD platelet unit had a mean of 4.8×10^{11} platelets per collection. A RD platelet unit generally comprised 6 to 8 units (mean 6.8) platelet concentrates, with an average yield of 0.8×10^{11} platelets/unit.</p> <p>Platelet type: Both apheresis and pooled platelet components were given in equal proportions</p>
Outcomes	<p>Primary Outcome: Unstated</p> <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Mild and severe bleeding episodes • Number of platelet transfusions received • Platelet increments following transfusion • Incidence of platelet refractoriness (alloimmunisation) • Mortality due to bleeding <p>Number of days on study: Mean days on study was 42 days (defined as when the platelet count was $< 50 \times 10^9/L$).</p>
Bleeding scale	<p>No bleeding scale was stated. Mild bleeds were defined as those not requiring active intervention</p> <p>Definition of significant bleeding: Not stated.</p>

	Definition of life-threatening bleeding: Not stated.	
Bleeding assessment	Participants were assessed clinically on a daily basis for signs of bleeding. Twice-daily fundoscopic examinations were performed once the platelet count was < 20 x 10 ⁹ /L	
Red cell transfusion policy	Not reported	
Notes	Published in abstract form only. Author contacted and provided additional unpublished material Participants randomised at: When platelet count < 50 x 10 ⁹ /L. Follow-up of participants: Participants were followed throughout their initial hospital stay and all subsequent admissions Stopping guidelines: Not reported. Power calculation: Not reported. Funding: Grants from the Vancouver Foundation and Mr and Mrs P.A. Woodward's Foundation Declarations of interest: Not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The study author reported that randomisation was performed using 25 envelopes, each with four cards inside: 1) therapeutic (T)/blood bank (BB)/random-donor platelets, 2) T/single donor (SD), 3) prophylactic (P)/BB, and 4) P/SD. As participants were enrolled, their allocation was drawn from the envelope. Once all four cards in each envelope were used, a new envelope was opened. However, if randomisation was performed by this method, there should have been 25 participants in each group, yet there are unbalanced numbers of participants between groups
Allocation concealment (selection bias)	High risk	Study investigators enrolling participants could possibly foresee study group assignment with this method of randomisation, and this could introduce selection bias
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	No mechanism mentioned to blind outcome assessors to study group assignment. Owing to the nature of the intervention, participants would be aware of study group assignment

Grossman 1980 (Continued)

Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	No mechanism mentioned to blind physicians to study group assignment. Owing to the nature of the intervention, participants would be aware of study group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment
Selective reporting (reporting bias)	Unclear risk	No study protocol was available. Red cell transfusion and white cell transfusion were reported in the abstract but not in the final manuscript. The significance of this is not clear. It is not clear whether these were secondary outcomes of interest
Other bias	Unclear risk	Reporting interim data analysis in the abstract may have changed the behaviour of the treating clinicians. The method of randomisation should have resulted in equal numbers between treatment arms, and yet there were unbalanced numbers in the different treatment groups
Protocol Deviation balanced?	Unclear risk	No study protocol was available. Eight participants were given 25 therapeutic-only transfusions because alloimmunisation made it impossible to maintain the platelet count $> 20 \times 10^9/L$

Murphy 1982

Methods	Parallel RCT (conducted from 1 July 1972 to 1 January 1976). Single centre. USA
Participants	<p>Inclusion criteria: Children with previously untreated acute leukaemia cared for at the Children's Hospital of Philadelphia</p> <p>Exclusion criteria: Not stated</p> <p>N = 56 children</p> <p>Arm 1 (Therapeutic): N = 21, ALL = 15; ANLL = 6</p> <p>Arm 2 (Prophylactic): N = 35, ALL = 28; ANLL = 7</p>
Interventions	<p>Comparison between therapeutic-only and prophylactic platelet transfusions</p> <p>Arm 1 (Therapeutic): Only given platelets in presence of 5 clinical indications</p> <ol style="list-style-type: none"> 1. Epistaxis not controlled by initial packing 2. Gross gastrointestinal bleeding 3. Gross genitourinary tract bleeding 4. Any central nervous system bleeding 5. Any bleeding episode felt to be life-threatening <p>Arm 2 (Prophylactic): Aim to maintain platelet count above $20 \times 10^9/L$</p>

	<p>Reasons to change a platelet transfusion trigger: Not reported. It is unclear whether platelets were given in both arms if clinical indications occurred and platelet count $> 20 \times 10^9/L$.</p> <p>Platelet dose: 4 units/m². Number of platelets/unit not stated.</p> <p>Platelet type: Pooled RD platelets.</p>
Outcomes	<p>Primary outcome: Survival</p> <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Number, duration, and dates of serious bleeding events (bleeds) during study • Total number of days in which bleeding was present • Platelet transfusion requirements in first 10 months (number of participants transfused; number of transfusions given; number of units given; number of participants bleeding; number of days with bleeding) • Platelet refractoriness <p>Number of days participants on study: Bleeding outcomes and platelet transfusion requirements were reported for first 10 months of study</p> <p>Average number of months/participants on study</p> <ul style="list-style-type: none"> • Arm 1: Mean length of follow-up 19.9 months (ALL = 20.7 months; ANLL = 16.6 months) • Arm 2: Mean length of follow-up 20.4 months (ALL = 21.6 months; ANLL = 17.3 months)
Bleeding scale	<p>No bleeding scale was stated.</p> <p>An episode was recorded as a bleed if it fulfilled the criteria, irrespective of the platelet count</p> <p>Bleeding was defined as:</p> <ul style="list-style-type: none"> • Nasal or oral bleeding requiring packing • Gross gastrointestinal haemorrhage • Gross genitourinary tract bleeding • Any central nervous system bleeding • Any bleeding episode felt to be life-threatening <p>Uncomplicated dermal bleeding was not included.</p> <p>If bleeding persisted for > 1 day without cessation, or if there was simultaneous bleeding from > 1 site, it was counted as 1 bleed</p> <p>Definition of significant bleeding: Not reported.</p> <p>Definition of life-threatening bleeding: Not reported.</p>
Bleeding assessment	Method not reported
Red cell transfusion policy	Not reported
Notes	<p>Participants randomised at: Not reported.</p> <p>Follow-up of participants: Until death or until 1 July 1976.</p> <p>Stopping rules: Not reported.</p> <p>Power calculation: Not performed.</p> <p>Funding: NIH research grant, Pediatric Cancer Center grant, and an appropriation from the Commonwealth of Pennsylvania</p> <p>Declarations of interest: Not reported.</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random allocation not described. Randomisation was performed separately for ALL and ANLL. Initially randomisation 1:1; changed to 2:1 after interim analysis 2 years after start of trial, since a preliminary analysis indicated that "the incidence of bleeding might be reduced in the prophylactic group" (further details of numbers enrolled prior to change in method of allocation not provided)
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not mentioned
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	No mechanisms mentioned to blind outcome assessors (presumed also to be clinicians) to treatment after allocation
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	No mechanisms mentioned to blind physicians to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment
Selective reporting (reporting bias)	High risk	Reported in text that there was "no correlation of the incidence of bleeding with sex, pre-transfusion haematocrit, concomitant corticosteroid therapy or the use of specific antineoplastic drugs". None of these were reported further
Other bias	High risk	Small study size with unbalanced numbers between groups with a greater proportion of ANLL in therapeutic-only group. Age and gender of participants for each group not reported
Protocol Deviation balanced?	Unclear risk	Not reported

Sintnicolaas 1982

Methods	Randomised trial (enrolment period not reported). Study performed by Haematological Supportive Care Project group in Netherlands
Participants	Inclusion criteria: Patients with acute leukaemia and severe thrombocytopenia N = 12
Interventions	Comparison between therapeutic-only and prophylactic platelet regimens Arm 1: Transfusion for “haemorrhage only” Arm 2: Prophylactic platelets to maintain platelet count above $20 \times 10^9/L$ Platelet dose: 4×10^{11} platelets/transfusion
Outcomes	No primary or secondary outcomes reported. Reported decreased morbidity in the prophylactic group (no deaths due to bleeding) Reported that 2 participants became refractory to platelets (1 in each arm)
Bleeding scale	Not reported
Bleeding assessment	Not reported
Red cell transfusion policy	Not reported
Notes	Published in abstract form only Participants randomised at: Not reported. Follow-up of participants: Not reported. Stopping rules: Not reported. Power calculation: Not reported. Funding: Not reported. Declarations of interest: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	Not reported
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only reported as an abstract

Selective reporting (reporting bias)	Unclear risk	Only reported as an abstract
Other bias	High risk	Only reported as an abstract. Small number of participants in this study reduces the likelihood that participants were equivalent at baseline between both arms. Numbers of participants in both study arms is not reported
Protocol Deviation balanced?	Unclear risk	Not reported

Solomon 1978

Methods	Parallel RCT (period of enrolment not reported). Single centre. USA
Participants	<p>Inclusion criteria: Previously untreated non-lymphoblastic acute leukaemia (age 16 to 71 years)</p> <p>Exclusion criteria: Promyelocytic leukaemia</p> <p>N = 31 successive patients receiving induction chemotherapy</p> <p>Arm 1: (Therapeutic): N = 12 patients receiving 17 courses of chemotherapy</p> <p>Arm 2: (Prophylactic): N = 19 patients; 17 patients included in analyses (2 patients died on day 1 of the study from cerebral haemorrhage) received 22 courses of chemotherapy</p>
Interventions	<p>Comparison of a therapeutic-only versus a prophylactic platelet regimen.</p> <p>Arm 1 (Specific indications): clinically significant bleeding or a 50% fall in platelets to below $20 \times 10^9/L$ occurred over 24 hrs.</p> <p>Arm 2 (Prophylactic): If platelet count $< 20 \times 10^9/L$.</p> <p>Reasons to change a platelet transfusion trigger: Both arms received platelets when there was clinically significant bleeding</p> <p>Platelet dose: Not reported.</p> <p>Platelet type: RD pooled platelets.</p>
Outcomes	<p>Primary outcome not reported.</p> <p>Outcomes reported:</p> <ul style="list-style-type: none"> Deaths (within 1 month of chemotherapy course) Deaths due to bleeding (within 1 month of chemotherapy course) Complete remission rates (time period not stated) Transfusion requirements (platelets, red cells) per course of chemotherapy <p>Average number of days on study: Not reported.</p>
Bleeding scale	<p>Not reported.</p> <p>Definition of significant or life-threatening bleeding: Not reported.</p>
Bleeding assessment	Not reported
Red cell transfusion policy	Not reported

Notes	Main author died before full publication Participants randomised at: Not reported. Follow-up of participants: Not reported. Stopping rules: Not reported. Power calculation: Not reported. Funding: Not reported. Declarations of interest: Not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random allocation not described: "17 randomly selected patients were given platelet transfusions"
Allocation concealment (selection bias)	Unclear risk	Attempt to conceal allocation not mentioned
Blinding (performance bias and detection bias) Assessor of bleeding assessment	Unclear risk	No mechanisms mentioned to blind outcome assessors (presumed also to be clinicians) to treatment after allocation
Blinding (performance bias and detection bias) Physician/Medical Staff	Unclear risk	No mechanisms mentioned to blind clinicians
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study not sufficiently reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Small number of participants in this study with unbalanced numbers in each study arm reduces the likelihood that participants were equivalent at baseline
Protocol Deviation balanced?	Unclear risk	Not reported

Stanworth 2013

Methods	Open-label, parallel, RCT (conducted from August 2006 to August 2011). Multi-centre study (12 centres). United Kingdom and Australia
Participants	Inclusion criteria: Patients aged 16 years or older. Have a confirmed diagnosis of a haematological malignancy. Have received or are going to receive myelosuppressive chemotherapy during this hospital admission with or without haematopoietic stem cell sup-

	<p>port (including patients undergoing HSCT - autograft or allograft). Thrombocytopenic or expected to become thrombocytopenic with a platelet count less than $50 \times 10^9/L$ for at least 5 days. Able to comply with treatment and monitoring</p> <p>Exclusion criteria: A WHO Grade 3 or 4 bleed during any stage of their treatment to date. A WHO Grade 2 bleeding episode during their current admissions. Any inherited haemostatic or thrombotic disorder (e.g. haemophilia). On regular aspirin (or related drugs) or will require regular therapeutic doses of anticoagulants (e.g. heparin), during the whole period of thrombocytopaenia. Acute promyelocytic leukaemia. Known HLA antibodies. Pregnant. Prior randomisation in this trial</p> <p>N = 600 participants were randomised (598 were included in the analysis, 2 were lost to follow-up)</p> <p>Arm 1 (No prophylaxis group): N = 301, AML = 55; ALL = 5; CML = 1; lymphoma = 102; myeloma = 125; other = 13</p> <p>Arm 2 (Prophylaxis group): N = 299, AML = 55; ALL = 1; CML = 2; lymphoma = 104; myeloma = 124; Other = 13</p>
Interventions	<p>Comparison between prophylactic and no-prophylactic platelet transfusions</p> <p>Arm 1 (No prophylaxis): Platelet transfusions were not given if the platelet count was $< 10 \times 10^9/L$</p> <p>Arm 2 (Prophylaxis): Prophylactic platelet transfusions were given at a threshold platelet count of $< 10 \times 10^9/L$</p> <p>Reasons to change a platelet transfusion trigger:</p> <p>Therapeutic platelet transfusions were given in both groups:</p> <ul style="list-style-type: none"> • If objective and documented signs or symptoms of WHO Grade 2, 3, or 4 bleeding • Prior to planned invasive procedures in keeping with current platelet transfusion guidelines (e.g. at least $50 \times 10^9/L$ for procedures such as lumbar punctures, insertion of indwelling lines, transbronchial biopsy, and laparotomy and at least $100 \times 10^9/L$ for operations in critical sites such as brain and eyes • Given at physician's discretion (rationale recorded) <p>Platelet dose: A single dose of "one adult unit" was given for prophylactic platelet transfusions and WHO Grade 2 bleeds. In participants with WHO Grade 3 or 4 bleeding, the attending haematologist decided the dose</p> <p>Platelet type: Both apheresis and pooled platelet components were given. Apheresis components were given in approximately 80% of cases</p>
Outcomes	<p>Primary outcome: The proportion of participants who experienced WHO Grade 2, 3, or 4 bleeding event up to 30 days from randomisation</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Number of participants who developed WHO Grade 3 or 4 bleeds within 30 days of randomisation • All-cause mortality within 30 days of randomisation • Time from randomisation to first WHO Grade 2, 3, or 4 bleeds • The rate of Grade 2, 3, or 4 bleeds up to 30 days from randomisation • The proportion of participants who received at least 1 platelet transfusion up to 30 days from randomisation • Total number of platelet transfusion episodes and units up to 30 days from randomisation • Total number of red cell transfusion episodes and units up to 30 days from

	<p>randomisation</p> <ul style="list-style-type: none"> • Number of days with a platelet count of $< 20 \times 10^9/L$ up to 30 days from randomisation • Time from randomisation until recovery from thrombocytopenia (platelet count $> 50 \times 10^9/L$ and maintained for 3 consecutive days without platelet transfusion support) • Number of days in hospital up to 30 days from randomisation • Adverse events related to transfusion <p>Number of days participantson study: Median number of days on study in the no-prophylaxis group was 30 days (IQR 29 to 30) and 30 days in the prophylactic group (IQR 30 to 30)</p>
Bleeding scale	<p>Modified WHO grading scale:</p> <p>Grade 1: Petechiae/purpura that is localised to 1 or 2 dependent sites, or sparse/non-confluent; oropharyngeal bleeding, epistaxis < 30 minutes duration</p> <p>Grade 2: Melaena, haematemesis, haemoptysis, fresh blood in stool, musculoskeletal bleeding, or soft tissue bleeding not requiring red cell transfusion within 24 hours of onset and without haemodynamic instability; profuse epistaxis or oropharyngeal bleeding, i. e. > 30 minutes in continuous duration; symptomatic oral blood blisters, i.e. bleeding or causing major discomfort; multiple bruises, each > 2 cm or any $1 > 10$ cm; petechiae/purpura that is diffuse or numerous, or > 5 distinct purpuric lesions; visible blood in urine; abnormal bleeding from invasive or procedure sites; unexpected vaginal bleeding saturating more than 2 pads with blood in a 24-hour period; bleeding in cavity fluids evident macroscopically; retinal haemorrhage with/without visual impairment</p> <p>Grade 3: Melaena, haematemesis, haemoptysis, haematuria - including intermittent gross bleeding without clots, abnormal vaginal bleeding, fresh blood in stool, epistaxis and oropharyngeal bleeding, bleeding from invasive sites, musculoskeletal bleeding, or soft tissue bleeding requiring red cell transfusion specifically for support of bleeding within 24 hours of onset and without haemodynamic instability; bleeding in body cavity fluids grossly visible; cerebral bleeding noted on CT without neurological signs and symptoms</p> <p>Grade 4: Debilitating bleeding including retinal bleeding and visual impairment (visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consultation); non-fatal cerebral bleeding with neurological signs and symptoms; bleeding associated with haemodynamic instability (hypotension, > 30 mmHg change in systolic or diastolic BP); fatal bleeding from any source</p> <p>Definition of significant bleeding</p> <p>Clinical bleeding was defined as bleeding of WHO Grade 2 or higher</p>
Bleeding assessment	<p>A local research nurse who was separate to the clinical unit nursing and medical staff performed the bleeding assessment (unblinded). Participants who were discharged home during the follow-up period completed bleeding diaries. There were pre-agreed definitions of types of bleed and guide notes to help the completion of bleeding assessment in a standardised fashion</p> <p>Grading of bleeding (based on completed bleeding assessment forms) was performed by a computer algorithm at the time of data entry</p>
Red cell transfusion policy	<p>In the absence of blood loss due to bleeding, a haemoglobin level of less than 90 g/L</p>

Notes	<p>Participants randomised at: When a consented patient's platelet count fell to $< 50 \times 10^9/L$.</p> <p>Follow-up of participants: 30 days after randomisation or death.</p> <p>Stopping rules: Not reported.</p> <p>Power calculation: Yes. The original power calculation considered the final sample sizes that would be required to demonstrate non-inferiority between the 2 arms for an estimated baseline rate of 20%. The margin of non-inferiority was based on the difference in the percentage of bleeds that would not be considered clinically important. It was agreed that an increase of up to 10% would be acceptable. With a 90% power, and a one-sided type 1 error rate (chance of wrongly declaring non-inferiority) of 5%, 280 participants will be required for analysis in each arm. This was rounded up to 300 participants in each arm. After manual review of the clinical bleeding assessment on 128 participants, the event rate in the prophylaxis arm was 45%. In light of these findings, it was agreed that the margin of non-inferiority could be extended from 10% to 15%. With these revised parameters, for a study with power 90% and type 1 error rate 5% (one-sided), the original sample size of 300 in each arm should be adequate</p> <p>Funding: National Health Service Blood and Transplant Research and Development Committee and the Australian Red Cross Blood Service</p> <p>Declarations of interest: Dr. Soutar reports serving on an advisory board for Celgene and receiving lecture fees from Chugai Pharmaceutical. Dr. Raj reports receiving lecture fees from Celgene and travel support from Therakos, a Johnson & Johnson company. Dr. Plews reports receiving travel support from Roche</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred into 2 groups in a 1:1 ratio using an independent centralised computerised randomisation service (telephone-based until 2009 and then Internet-based). The first 10 participants were assigned with the use of simple randomisation. The remaining participants were assigned with the use of minimisation. Minimisation factors were study centre, diagnosis, and treatment plan
Allocation concealment (selection bias)	Low risk	Allocation concealment was performed by an independent centralised computerised randomisation service
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Owing to the nature of the intervention, the research nurses (assessor of inpatient bleeding) and participant (initial reporter of outpatient bleeding) were aware of study group assignment and treatment. Bleeding assessors were independent from the clini-

		cal decision as to whether or not a platelet transfusion was required. The assessment of bleeding was converted to a bleeding grade using a validated computer algorithm
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Owing to the nature of the intervention, participants and clinicians were aware of study group assignment. Participants who were discharged home during the follow-up period completed bleeding diaries. If participants reported bleeding, the research nurses completed clinical bleeding assessment forms at the next hospital visit. All written descriptions of bleeding episodes were examined by 2 assessors who were unaware of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Days with missing bleeding assessments were accounted for with the use of a multiple-imputation approach. Sensitivity analyses were performed to assess the robustness of the primary analysis with respect to missing data. Bleeding assessments were completed on 93% of study days (8405 of 9030 days) for participants in the no-prophylaxis group and on 97% of study days (8733 of 8970) in the prophylaxis group
Selective reporting (reporting bias)	Low risk	On review of study protocol, all the study's prespecified study outcomes were reported
Other bias	Low risk	Potential heterogeneity between assessment of bleeding at different participating centres was mitigated by training of bleeding assessors prior to their performing any bleeding assessments and training updates at regular intervals throughout the trial Prior to initiation of data collection, all local research staff completing the daily bleeding assessments received standardised face-to-face training from a small core of research staff. They also had pre-agreed definitions of types of bleed and guide notes to help them complete the bleeding assessment in a standardised fashion (Stanworth 2010). Six-monthly educational meetings were also held centrally for all research nurses and staff, which included scenarios for assessing bleeding as part of a strategy

		to standardise the approach to conducting bleeding assessments. A monthly newsletter provided updates on training issues. Duplicate assessments of bleeding scores were undertaken during monitoring site visits conducted by the central coordinating staff
Protocol Deviation balanced?	Low risk	Most transfusions in both groups were given according to protocol (89% (450 of 504 transfusions) in the no-prophylaxis group and 91% (810 of 894) in the prophylaxis group). The proportion of participants who received all transfusions according to protocol was slightly higher in the no-prophylaxis group (86% (258 of 300 participants)) than in the prophylaxis group (77% (230 of 298))

Wandt 2012

Methods	Open-label, parallel RCT (conducted from 1 February 2005 to 31 May 2010). Multi-centre, single-country. Germany
Participants	<p>Inclusion criteria: Hospital inpatients during study</p> <p>(AML group):</p> <ul style="list-style-type: none"> • Inclusion in studies of the Deutsche Studien-Initiative Leukämie (DSIL) and Ostedetusche Studiengruppe Hämatologie/Onkologie (OSHO) for AML • AML M3/M3v can be included only when in complete remission • Age 16 to 80 years • Signed consent form (by parent/guardian for minors) <p>(Autologous group):</p> <ul style="list-style-type: none"> • AML and ALL patients in first or second remission • Low-grade or high-grade non-Hodgkin lymphoma or morbus Hodgkin or multiple myeloma • Conditioning regimen: TBI 8-12 Gy/Cy 120 or BEAM or BU/CY or melphalan 140 to 200 mg/m² or a similarly intensive chemotherapy regimen • Age 16 to 65 years <p>Exclusion criteria</p> <p>(Both groups):</p> <ul style="list-style-type: none"> • Known refractoriness to platelet transfusion • Known major bleeding with thrombocytopenia when the reason for bleeding is still ongoing • Known plasmatic coagulation disorder • Patient unable to give informed consent <p>(Autologous group):</p> <ul style="list-style-type: none"> • Patients with pulmonal or cerebral lesions due to infection or neoplasm • Patients with light-chain (AL) amyloidosis <p>N = 396 participants were randomised (391 were included in the analysis, 1 was lost to</p>

	<p>follow-up, and 4 did not receive allocated intervention)</p> <p>Arm 1: N = 197, AML = 94; autologous HSCT = 103</p> <p>Arm 2: N = 194, AML = 96; HSCT = 98</p>
Interventions	<p>Comparison of therapeutic-only platelet transfusion versus routine prophylactic platelet transfusion</p> <p>Arm 1 (Therapeutic): Platelet transfusions only when “clinically relevant” bleeding occurred, defined as bleeds of Grade 2 or higher according to modified WHO criteria</p> <p>Arm 2 (Prophylactic): Participants were transfused prophylactically when the morning platelet count was $10 \times 10^9/L$ or lower.</p> <ul style="list-style-type: none"> • Platelet transfusion according to protocol started at day 1 after the end of induction chemotherapy, or at day 1 of each consolidation cycle in group A, and at the day of stem-cell transplantation in group B <p>Reasons to change a platelet transfusion trigger:</p> <p>Prophylactic platelet transfusion at platelet counts of $10 \times 10^9/L$ or lower was recommended when sepsis or infections with an increased bleeding risk, such as invasive fungal infection or plasmatic coagulopathy (e.g. disseminated intravascular coagulation or hyperfibrinolysis) were present</p> <p>Platelet dose: One platelet unit. If bleeding continued despite 1 platelet transfusion, further transfusions were given according to the decision of the treating physician</p> <p>Platelet type: Both SD apheresis platelets and pooled platelet concentrates were used</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • Number of platelet transfusions given during a standardised observation time of 14 days per participant <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Incidence of clinically relevant bleeding • Time to onset of clinically relevant bleeding • Percentage of days in which participants had bleeds of Grade 2 or higher, dependent on morning platelet count • Days with platelet counts less than $20 \times 10^9/L$ • Side effects of transfusions • Duration of hospitalisation • Survival <p>Average number of days participants on study: Not reported.</p>
Bleeding scale	<p>Modified WHO grading scale</p> <p>Grade 2: Any oral or nasal bleeding that could not be treated at the bedside by a nurse, or that was unpleasant for the patient; spontaneous haematoma in deep tissues, joint bleeding; haematochezia, melanotic stool (proven by faecal blood test), haematemesis; visible haematuria, abnormal vaginal bleeding more than spotting; haemoptysis and bloody sputum with no nasal or oropharyngeal bleeding; bleeding at venepuncture sites, intravenous lines; other bleeding as described in the clinical report form</p> <p>Grade 3: Any oral, nasal, skin, soft tissue, musculoskeletal, gastrointestinal, genitourinary, pulmonary, invasive site bleeding or other bleeding necessitating transfusion of red blood cells over routine needs within 24 hours</p> <p>Grade 4: Any oral, nasal, skin, soft tissue, musculoskeletal, gastrointestinal, genitourinary, pulmonary, invasive site bleeding or other site bleeding necessitating transfusion of red blood cells and associated with severe haemodynamic instability necessitating in-</p>

	<p>tensive care; any fatal bleeding; retinal bleeding with visual impairment proven by fundoscopy, CNS symptoms and sudden headache showing CNS bleeding on CT, any fatal CNS bleeding</p> <p>Definition of significant bleeding: Clinically relevant bleeding was defined as bleeds of Grade 2 or higher according to modified WHO criteria</p> <p>Definition of life-threatening bleeding: Not stated.</p>	
Bleeding assessment	Twice-daily bleeding assessments performed by a physician or experienced nurse. The treating haematologist was responsible for documentation and reporting in each centre. Two investigators masked to treatment strategy transformed the bedside bleeding report into modified WHO categories	
Red cell transfusion policy	Given to maintain haemoglobin concentrates at 80 g/L or higher	
Notes	<p>Participants randomised at: Not reported.</p> <p>Follow-up of participants: The study was completed when the platelet count was self sustaining at more than 20 x 10⁹/L for 2 days or a maximum of 30 days, at hospital discharge, when treatment failure was diagnosed, at death, or at study withdrawal, whichever occurred first</p> <p>Stopping rules: Predefined stopping rule would only be applied if more than 2 fatal events happened that were clearly attributable to the new strategy</p> <p>Power calculation: Yes. The study was designed to have a minimum power of 90% to detect a clinically meaningful difference of 25% in the primary endpoint in the 2 subgroups separately for which 180 participants per group were needed</p> <p>Funding: Deutsche Krebshilfe eV (German Cancer Aid).</p> <p>Declarations of interest: No conflicts of interest.</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned using a computer-generated randomisation sequence with minimisation to randomly assign participants, in a 1:1 ratio, to the therapeutic-only or prophylactic platelet transfusion protocol
Allocation concealment (selection bias)	Low risk	Central allocation at the study centre with communication by fax
Blinding (performance bias and detection bias) Assessor of bleeding assessment	High risk	Assessors of bleeding assessment and participants undertaking interventions were not masked to group assignment. A physician or experienced nurse examined participants for bleeding, and the treating haematologist was responsible for documentation and reporting. Therefore the person assessing bleeding may also have been the per

		son deciding on the need for a platelet transfusion. Two investigators masked to treatment strategy transformed the bedside bleeding report into modified WHO categories
Blinding (performance bias and detection bias) Physician/Medical Staff	High risk	Investigators and physicians undertaking interventions were not masked to group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to allow assessment
Selective reporting (reporting bias)	Unclear risk	On review of the protocol, the secondary outcome "duration of thrombocytopenia below 10,000/ μ L" was not reported
Other bias	Unclear risk	Interim data from the study was reported prior to study completion Reporting interim data may have affected the behaviour of clinicians with regard to recruiting participants, assessing participants for bleeding, and prescription of platelet transfusions
Protocol Deviation balanced?	Unclear risk	In the therapeutic-only group, 140 platelet transfusions (22%) were not in accordance with the protocol, and in the prophylactic group platelet transfusions were not given 148 times (11%) despite a morning platelet count of less than $10 \times 10^9/L$

AA: aplastic anaemia
 ALL: acute lymphoblastic leukaemia
 AML: acute myeloid leukaemia
 ANLL: acute non-lymphoblastic leukaemia
 BB: blood bank
 BP: blood pressure
 CML: chronic myeloid leukaemia
 CNS: central nervous system
 CT: computerised tomography
 HLA: human leukocyte antigen
 HSCT: hematopoietic stem cell transplantation
 IQR: interquartile range
 RCT: randomised controlled trial
 RD: random donor
 SD: single donor
 WHO: World Health Organization

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

Study	Reason for exclusion
Aderka 1986	A non-randomised retrospective study
Agliastro 2006	Comparison of apheresis vs buffy -coat platelet transfusions (Abstract)
Akkök 2007	Comparison of apheresis vs buffy -coat platelet transfusions
Anderson 1997	Comparison of apheresis vs buffy -coat -derived vs platelet -rich plasma -derived platelet products
Andreu 2009	Review
Andrew 1993	Wrong patient group - premature infants
Arnold 2004	Comparison of apheresis vs whole -blood -derived platelet transfusions
Arnold 2006	Wrong patient group - i ntensive therapy unit
Avvisati 2003	Review
Bai 2004	Wrong patient group - solid tumours
Benjamin 2002	Review
Bentley 2000	Comparison of autologous vs allogeneic platelet transfusions
Blajchman 2008	Review
Blumberg 2002	Comparison of washed vs standard platelet transfusions
Blundell 1996	Comparison of standard vs 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 vs mismatched platelet products
Casbard 2004	Systematic review and wrong patient group
Chaoui 2005	Observational prospective study
Cid 2007	Systematic review of differing platelet transfusion doses

(Continued)

Couban 2002	Comparison of plasma reduction and leucodepletion
de Wildt-Eggen 2000	Comparison of platelet concentrates in plasma vs additive solution
Decaudin 2004	Non-randomised prospective study
Diedrich 2005	Comparison of prophylactic platelet transfusion if platelet count < 10 x 10 ⁹ /L vs if platelet count < 30 x 10 ⁹ /L
Diedrich 2009	Comparison of platelet products stored 1-5 vs 6-7 days
Dumont 2011	Comparison of buffy -coat vs 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
Follea 2004	Guideline
Franklin 1995	Comparison of different platelet doses
Friedmann 2002	A non-randomised retrospective analysis
Gajic 2006	Wrong patient group - intensive therapy 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 vs pooled platelet products
Gmür 1991	A non-randomised prospective cohort observational study (different platelet transfusion thresholds)
Goodnough 2001	Wrong comparator. Participants received platelet components from donors who had received differing doses of thrombopoietin
Goodnough 2002	Review
Goodnough 2005	Review
Goodrich 2008	Comparison of pathogen -inactivated vs standard apheresis platelets

(Continued)

Greeno 2007	A non-randomised prospective observational study (different platelet transfusion thresholds)
Gurkan 2007	Comparison of apheresis vs 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 vs T- Sol platelet transfusions
Heal 1993	Comparison of ABO -compatible vs mismatched platelet transfusions
Heal 2004	Review
Heckman 1997	Comparison of prophylactic platelet transfusion if platelet count $\leq 10 \times 10^9/L$ vs if platelet count $\leq 20 \times 10^9/L$
Heddle 1994	Comparison of plasma from platelet concentrates vs platelets
Heddle 1999	Comparison of plasma removal vs leucodepletion
Heddle 2002	Comparison of plasma removal vs leucodepletion
Heddle 2003	Systematic review - methods of assessing bleeding outcome
Heddle 2009	Comparison of low -dose platelet transfusion vs standard -dose platelet transfusion
Higby 1974	Comparison of prophylactic platelet transfusion vs platelet-poor plasma
Hoque 2013	Fewer than 80% of participants had a haematological malignancy and no additional subgroup data available from the author
ISRCTN49080246	Comparison of 1-5 vs 6-7 day -old platelet transfusions
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 vs pooled platelet concentrates
Kerkhoffs 2010	Comparison of standard platelets vs pathogen -inactivated platelets vs platelets stored in PAS II media
Klumpp 1999	A randomised cross-over study. This study was included within the previous systematic review. This study compared different platelet component doses and has been excluded from this review
Lapierre 2003	Comparison of standard apheresis platelet products vs a donor reduction policy

(Continued)

Lawrence 2001	A non-randomised retrospective historical control study (different platelet transfusion thresholds)
Leach 1991	Comparison of warmed vs standard platelet transfusions
Lee 1989	Comparison of ABO -matched vs 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 vs conventional platelet products
Lu 2011	Comparison of low -dose platelet transfusion vs standard -dose platelet transfusion
Martel 2004	Review
McCullough 2004	Comparison of pathogen -inactivated vs conventional apheresis platelets
McNicol 2003	Review
Messerschmidt 1988	Comparison of HLA -matched vs mismatched platelet transfusions
Mirasol 2010	Comparison of pathogen -inactivated vs conventional platelet products
Murphy 1986	Comparison of HLA -matched vs leucodepleted blood products
Navarro 1998	A non-randomised retrospective historical control observational study (different platelet transfusion thresholds)
NCT00180986	Comparison of varying platelet concentrate donors
NCT00699621	Wrong patient group - intracerebral haemorrhage
Nevo 2007	A non-randomised retrospective analysis (different platelet thresholds)
Norol 1998	A non-randomised prospective comparison (3 different doses of platelets)
Oksanen 1991	Comparison of pre- versus post -storage leucodepletion of platelet-rich plasma -derived platelet transfusions
Oksanen 1994	Comparison of leucodepleted buffy -coat -derived platelet transfusions vs historical control
Paananen 2009	Non-randomised study (unclear whether prospective or retrospective)

(Continued)

Pamphilon 1996	Comparison of non-leucodepleted multiple -donor non-apheresis buffy -coat platelets vs non-leucodepleted single -donor apheresis platelets or leucocyte -depleted single -donor apheresis platelets
Paramo 2004	Review
Poon 2003	Review
Qureshi 2007	Audit of platelet transfusions in the UK
Rabinowitz 2010	Review
Rayment 2005	Review
Rebulla 1997	Comparison of prophylactic platelet transfusion if platelet count $\leq 10 \times 10^9/L$ vs if platelet count $\leq 20 \times 10^9/L$
Reed 1986	Wrong patient group - massive transfusion
Roberts 2003	Review
Roy 1973	Comparison of standard -dose platelet transfusion vs high -dose platelet transfusion
Sagmeister 1999	A non-randomised retrospective study (aplastic anaemia)
Sakakura 2003	Review
Samama 2005	Guideline
Schiffer 1983	Comparison of leucodepleted vs standard platelet concentrates
Sensebe 2004	Comparison of standard -dose platelet transfusion vs high -dose platelet transfusion
Shanwell 1992	Comparison of fresh vs stored platelets
Shehata 2009	Systematic review - ABO -identical vs non-identical platelet transfusions
Shen 2007	Review
Singer 1988	Single -donor HLA -matched vs random -donor platelets
Sintnicolaas 1995	Comparison of leucocyte -depleted vs standard platelets
Slichter 2004	Review
Slichter 2006	Comparison of pathogen -inactivated vs conventional apheresis platelets
Slichter 2007	Review

(Continued)

Slichter 2010	Comparison of low -dose platelet transfusion vs intermediate -dose platelet transfusion vs high- dose platelet transfusion
Sosa 2003	Review
Speiss 2004	Wrong patient group - cardiac
Steffens 2002	Comparison of standard -dose vs high -dose platelet transfusion
Strauss 2004	Review
Strauss 2005	Review
Strindberg 1996	Comparison of apheresis vs buffy -coat platelet products
Sweeney 2000	Comparison of pre-storage leucodepleted vs bedside leucodepleted platelets
Tinmouth 2003	Review
Tinmouth 2004	Comparison of low -dose platelet transfusion vs standard -dose platelet transfusion
Tosetto 2009	Guideline
TRAP 1997	Comparison of standard pooled platelet product vs irradiated pooled platelet product vs leucodepleted pooled platelet product vs apheresis platelet product
Vadhan-Raj 2002	Wrong patient group - gynaecological malignancy
van Marwijk Kooy 1991	Comparison of leucodepleted platelet products prepared by filtration or centrifugation
van Rhenen 2003	Comparison of pathogen -inactivated vs standard buffy -coat -derived platelet transfusions
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 vs prophylactic platelet transfusions)
Wandt 2006	A non-randomised prospective study with an historical case control (therapeutic vs prophylactic platelet transfusions)
Wandt 2010	Review
Wang 2002	A comparison of acetaminophen and diphenhydramine vs placebo as premedication for platelet transfusions
Wang 2005	Review

(Continued)

Weigand 2009	Prospective observational study
Williamson 1994	Comparison of standard vs bedside leucodepleted platelet products
Woodard 2002	Review
Zahur 2002	Prospective observational study
Zeller 2014	Review
Zhao 2002	Comparison of leucodepleted vs standard platelet transfusions
Zumberg 2002	This study was included within the previous systematic review. However, because of 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

Characteristics of ongoing studies [ordered by study ID]

NCT01615146

Trial name or title	Outpatient Platelet Transfusions in Myelodysplastic Syndromes and Leukaemia: The OPTIMAL Pilot
Methods	Single-blind, parallel RCT. Single centre. Canada
Participants	<p>Inclusion criteria: Adults 18 years or older with documented MDS (including MDS subtype CMML) or AML (as defined by WHO criteria). Severe thrombocytopenia defined as a platelet count of $\leq 10 \times 10^9/L$ documented on 2 consecutive samples at least 7 days apart. Receiving outpatient-based supportive or palliative care including palliative cytoreductive, immunomodulatory, or hypomethylating therapy, e.g. hydroxyurea or low-dose cytarabine, lenalidomide, azacytidine, or decitabine. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • High-dose therapy in past 2 months, e.g. AML-type induction or consolidation therapy • Thrombocytopenia suspected to be due to immune or peripheral destruction • Splenomegaly, palpated at greater than 5 cm below the costal margin or greater than 20 cm on imaging • Alloimmune platelet refractoriness • Clinically relevant bleed (Grade 3 or higher) within the past 3 months • Coagulopathy (prothrombin time or activated partial thromboplastin more than 1.5 times the upper limit of normal or fibrinogen less than 2 g/L) • Require anticoagulant therapy, e.g. heparin, or antiplatelet therapy, e.g. aspirin • Significant renal impairment (creatinine more than 1.5 times the upper limit of normal) • Geographic inaccessibility resulting in the inability to comply with follow-up visits • Pregnant or breast-feeding • Unwilling or unable to provide informed consent

	Estimated study enrolment N = 60
Interventions	<p>Comparison between therapeutic-only and prophylactic platelet transfusion</p> <p>Arm 1 (Therapeutic): Participants will not receive routine prophylactic platelet transfusions. Platelet transfusions will be given to treat documented clinically relevant bleeding defined as WHO bleeding of Grade 2 or greater. Participants may be transfused at the discretion of the treating physician. The indication for all platelet transfusions will be recorded by asking the ordering physician</p> <p>Arm 2 (Prophylactic): Participants will receive a platelet transfusion when the measured platelet count is $< 10 \times 10^9/L$. Participants may receive additional platelet transfusions at the discretion of the treating physician. The indication for all platelet transfusions will be recorded</p> <p>Platelet dose and type: A single dose of random-donor platelets (4 unit pool or random-donor platelets or 1 apheresis unit)</p>
Outcomes	<p>Primary outcome measures: Feasibility [Time Frame: 18 months] [Designated as safety issue: No] Overall enrolment, off protocol transfusions per each randomised group, total number of platelet transfusions per group, and participant compliance with daily self assessment of bleeding will be evaluated</p> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> • Bleeding events between therapeutic-only and prophylactic transfusion groups [Time Frame: 6 month follow-up period] [Designated as safety issue: Yes] <p>Assessments will include:</p> <ul style="list-style-type: none"> • Non-cutaneous Grade 2 bleeding or higher by the WHO bleeding assessment scale 2 • Grade 3 bleeding or higher • Time from randomisation to first bleeding event of Grade 3 or higher • Total number of red cell transfusions per group • Total number of hospital days per group • Number of completed daily bleeding assessments per group • Quality of life • Mortality
Starting date	June 2012
Contact information	Elizabeth Chatelain, Ottawa Hospital, Canada
Notes	<p>NCT01615146</p> <p>Study is currently on hold due to poor study recruitment.</p> <p>Results are expected in the next year.</p>

AML: acute myeloid leukaemia

CMML: chronic myelomonocytic leukaemia

MDS: myelodysplastic syndrome

RCT: randomised controlled trial

WHO: World Health Organization

DATA AND ANALYSES

Comparison 1. Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with at least one bleeding episode	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of days with significant bleeding per patient	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants with severe or life threatening bleeding	2	801	Risk Ratio (M-H, Fixed, 95% CI)	4.91 [0.86, 28.12]
4 Time to first bleeding event (Hazard Ratio)	2		Hazard Ratio (Random, 95% CI)	Totals not selected
5 Mortality from all causes within 30 days from the start of the study	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Mortality due to bleeding within 90 days from the start of the study	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Mean number of platelet transfusions per patient	2	991	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.63, -0.37]
8 Mean number of red cell transfusions per patient	2	801	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.14, 0.36]
9 Proportion of patients requiring surgical or other intervention	2	991	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [0.44, 35.27]
10 Proportion of patients requiring additional medical interventions required to stop bleeding	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Proportion of patients requiring additional products to stop bleeding	2	991	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.55]
12 Patients achieving complete remission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Adverse effects of transfusion	2	991	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.62, 1.68]
14 Number of participants with at least one bleeding episode per disease category.	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Patients with Acute leukaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Patients with lymphoma or myeloma	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Patients with CML or other cancer	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

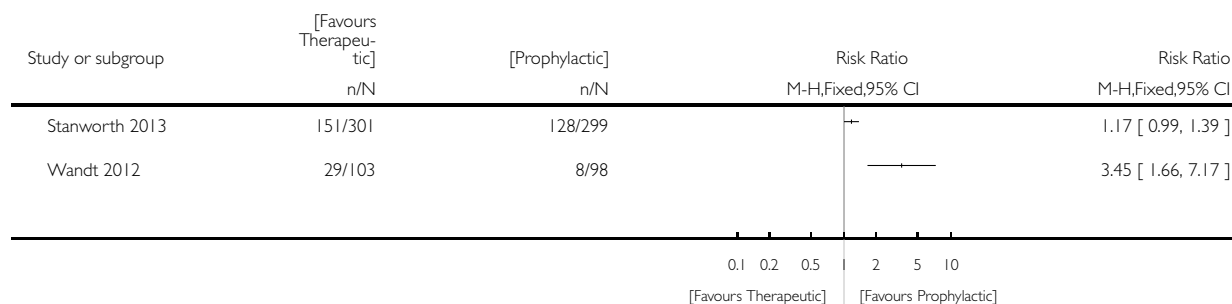
15	Number of participants with at least one bleeding episode per treatment category.	2	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1	Patients undergoing autologous haematopoietic stem cell transplantation	2	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2	Patients receiving chemotherapy	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3	Patients receiving allogeneic haematopoietic stem cell transplantation	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16	Number of days with significant bleeding per patient per treatment category	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1	Participants undergoing autologous haematopoietic stem cell transplantation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2	Participants receiving chemotherapy/allogeneic stem cell transplantation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17	Number of participants with severe or life threatening bleeding receiving autologous haematopoietic stem cell transplantation	2	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18	Number of participants with severe or life threatening bleeding receiving chemotherapy/allogeneic haematopoietic stem cell transplantation	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19	Time to first bleeding event per treatment category	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1	Participants undergoing autologous haematopoietic stem cell transplantation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2	Participants receiving chemotherapy/allogeneic stem cell transplantation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20	Number of participants with at least one bleeding episode per age category	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1	Age greater than or equal to 60 yrs	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2	Age 18 to less than 60 yrs	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 1 Number of participants with at least one bleeding episode.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

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

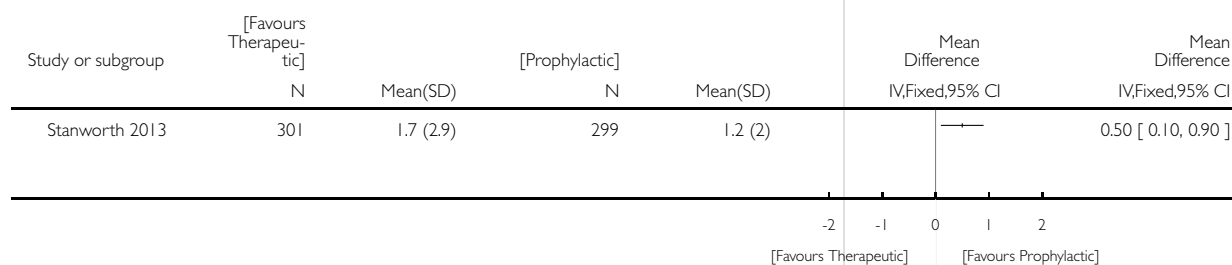


Analysis 1.2. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 2 Number of days with significant bleeding per patient.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 2 Number of days with significant bleeding per patient

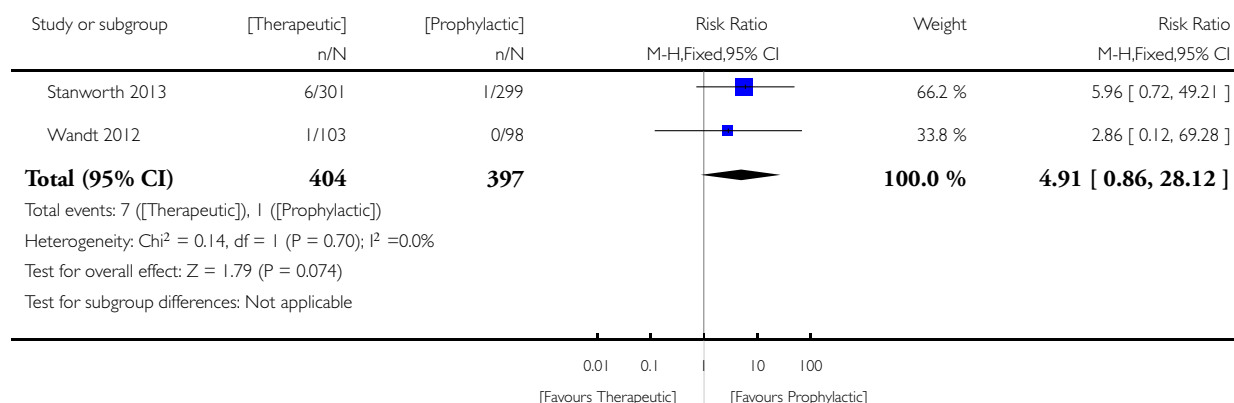


Analysis 1.3. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 3 Number of participants with severe or life threatening bleeding.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 3 Number of participants with severe or life threatening bleeding

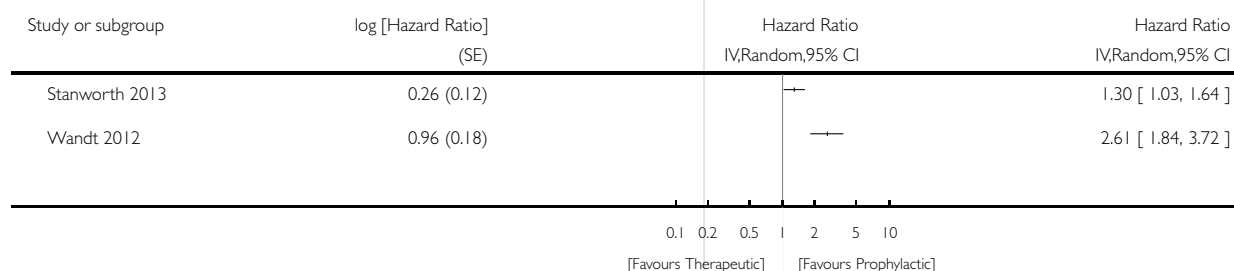


Analysis 1.4. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 4 Time to first bleeding event (Hazard Ratio).

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 4 Time to first bleeding event (Hazard Ratio)

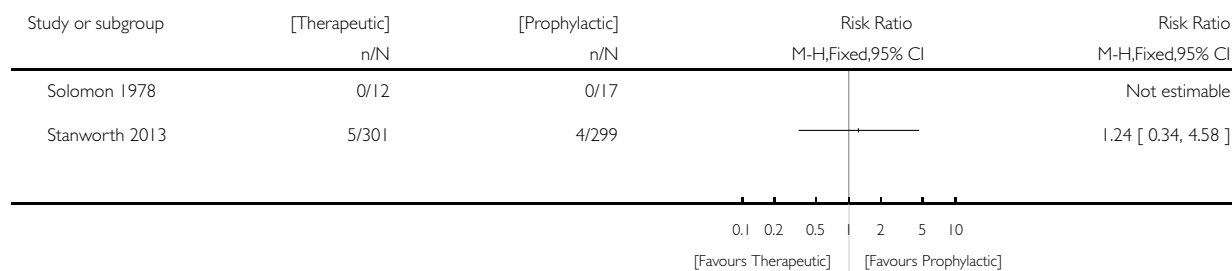


Analysis 1.5. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 5 Mortality from all causes within 30 days from the start of the study.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 5 Mortality from all causes within 30 days from the start of the study

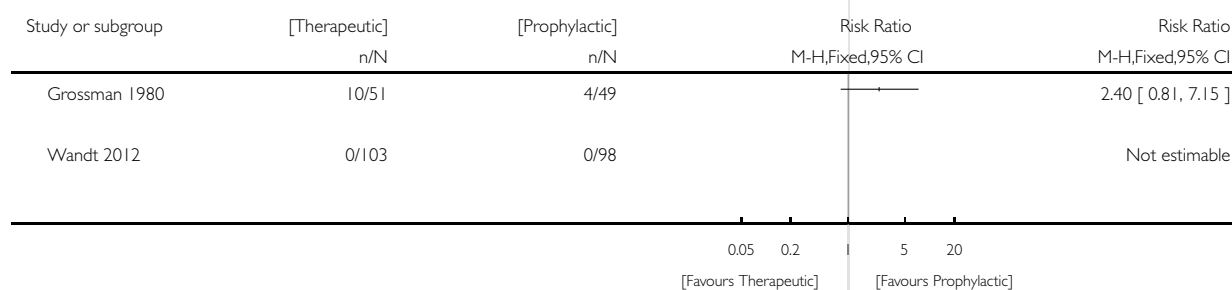


Analysis 1.6. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 6 Mortality due to bleeding within 90 days from the start of the study.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 6 Mortality due to bleeding within 90 days from the start of the study

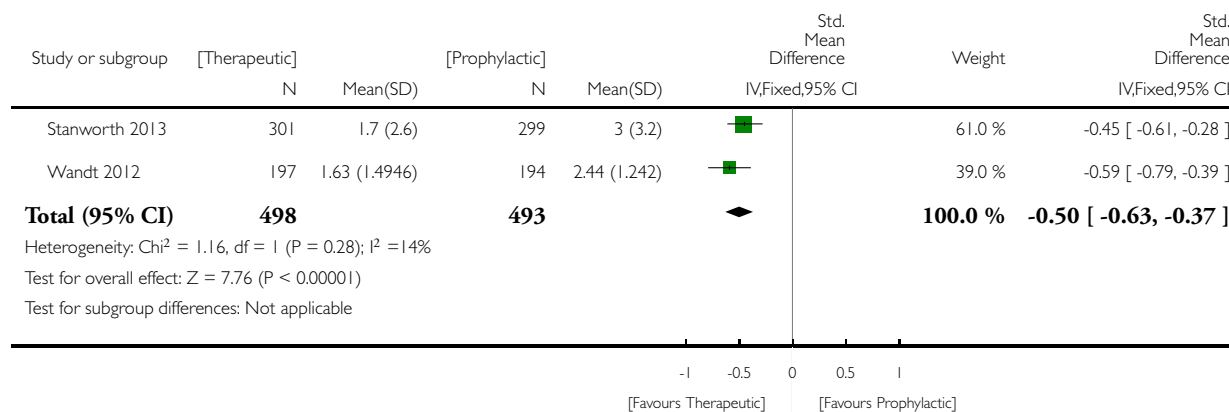


Analysis 1.7. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 7 Mean number of platelet transfusions per patient.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 7 Mean number of platelet transfusions per patient

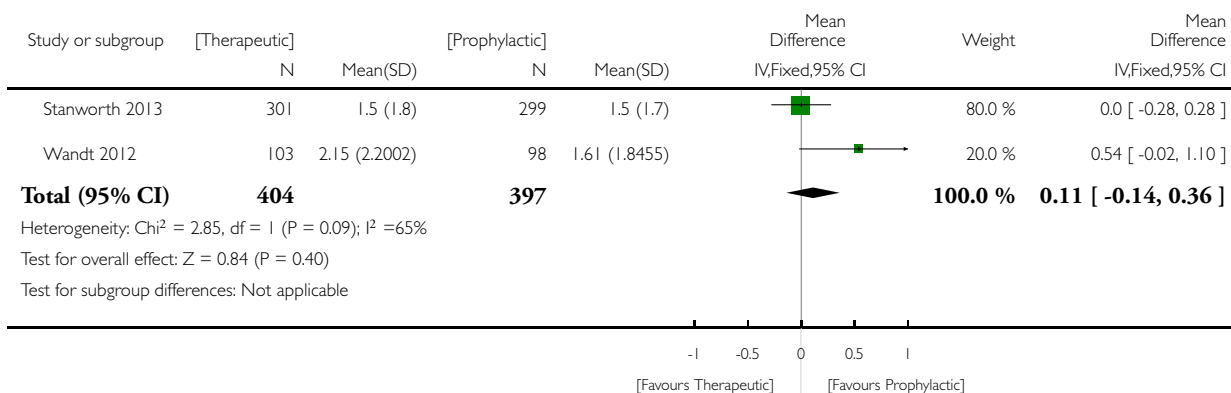


Analysis 1.8. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 8 Mean number of red cell transfusions per patient.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 8 Mean number of red cell transfusions per patient

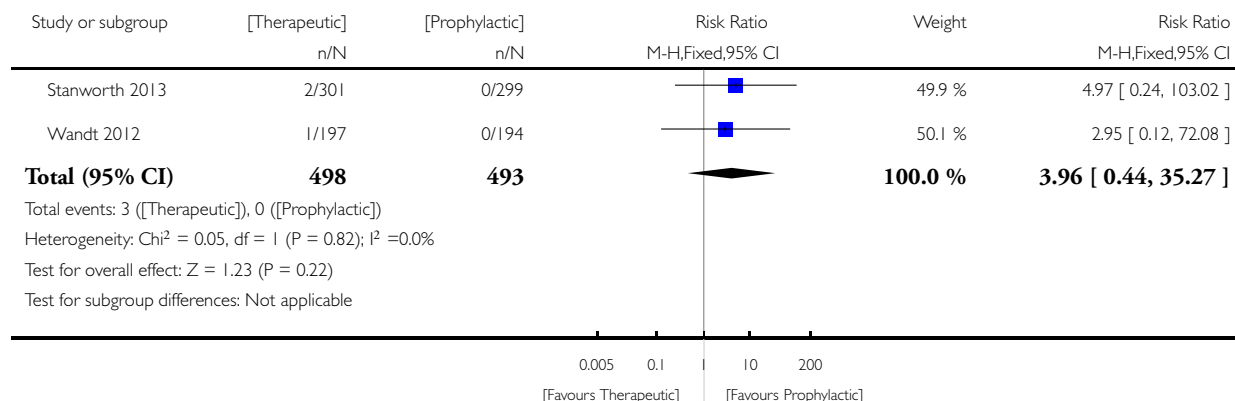


Analysis 1.9. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 9 Proportion of patients requiring surgical or other intervention.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 9 Proportion of patients requiring surgical or other intervention

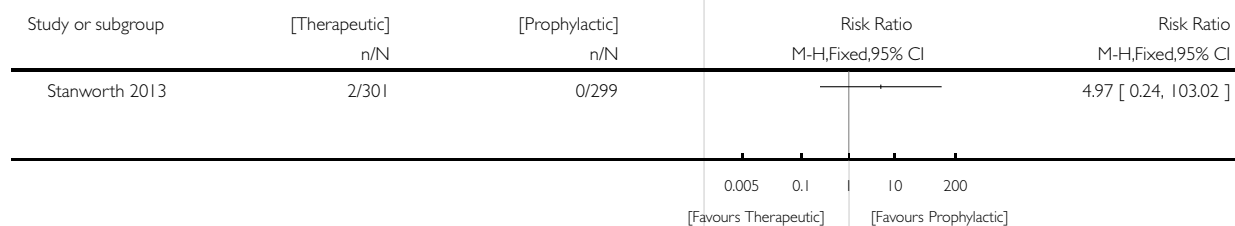


Analysis 1.10. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 10 Proportion of patients requiring additional medical interventions required to stop bleeding.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 10 Proportion of patients requiring additional medical interventions required to stop bleeding

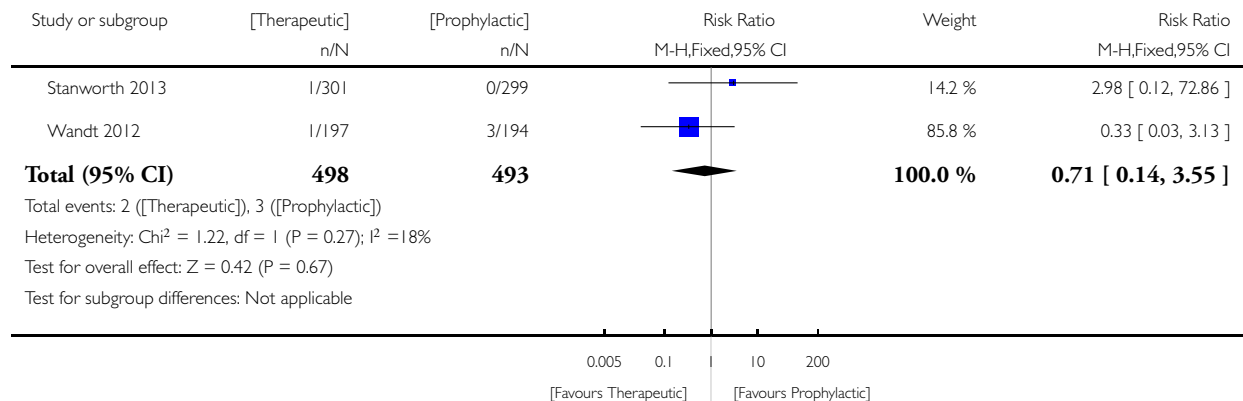


Analysis 1.11. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 11 Proportion of patients requiring additional products to stop bleeding.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 11 Proportion of patients requiring additional products to stop bleeding

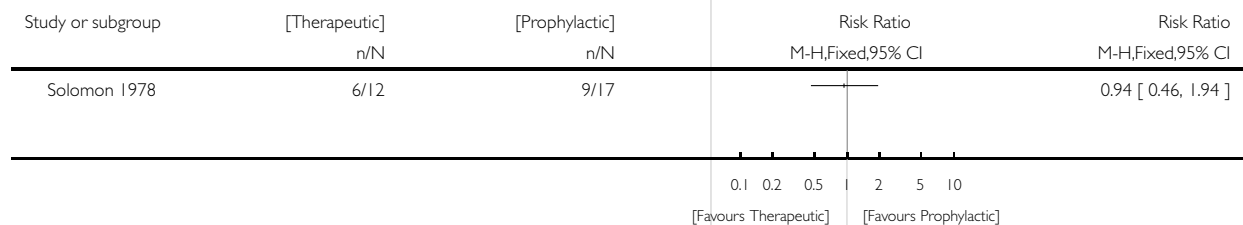


Analysis 1.12. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 12 Patients achieving complete remission.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 12 Patients achieving complete remission

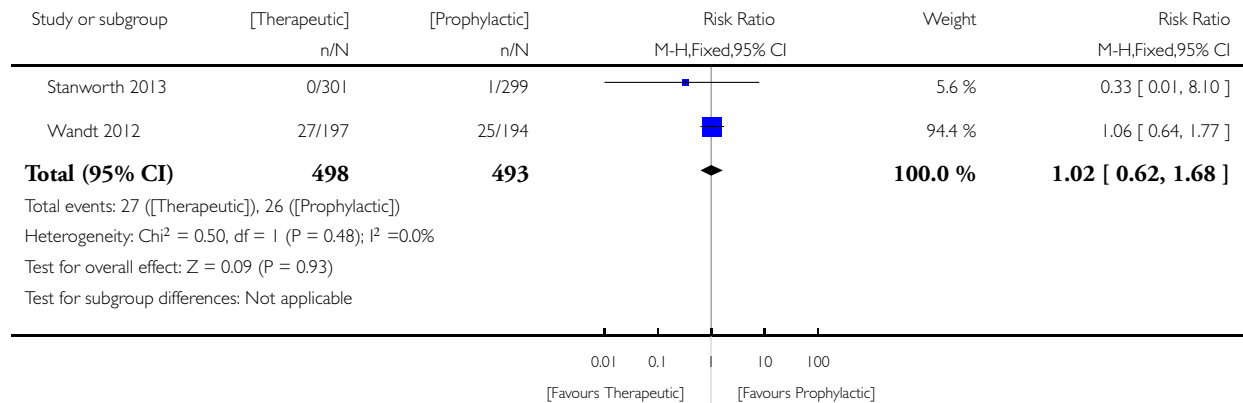


Analysis 1.13. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 13 Adverse effects of transfusion.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 13 Adverse effects of transfusion

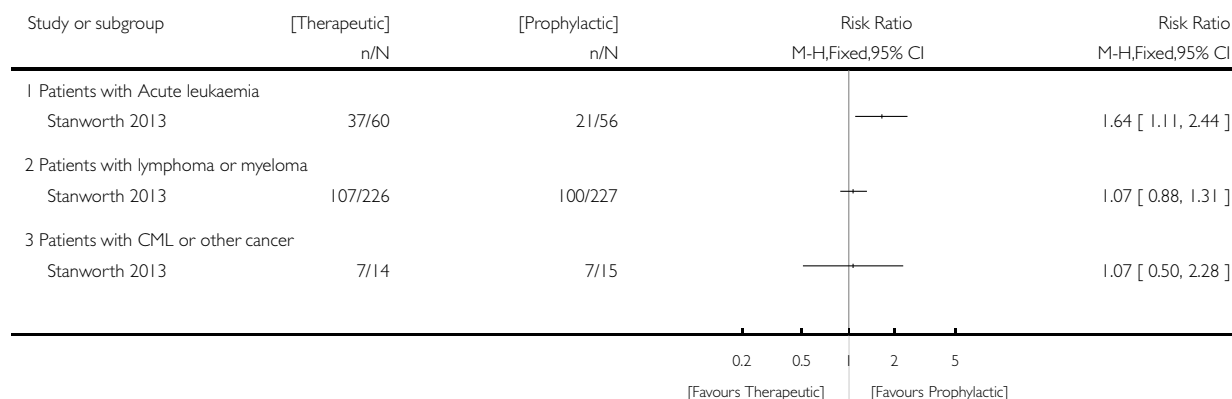


Analysis 1.14. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 14 Number of participants with at least one bleeding episode per disease category..

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 14 Number of participants with at least one bleeding episode per disease category.

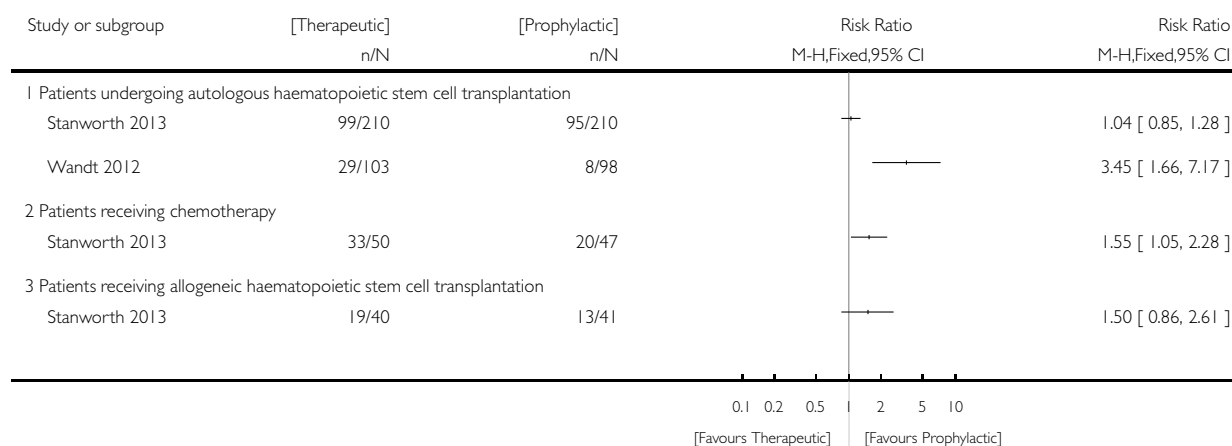


Analysis 1.15. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 15 Number of participants with at least one bleeding episode per treatment category..

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 15 Number of participants with at least one bleeding episode per treatment category.

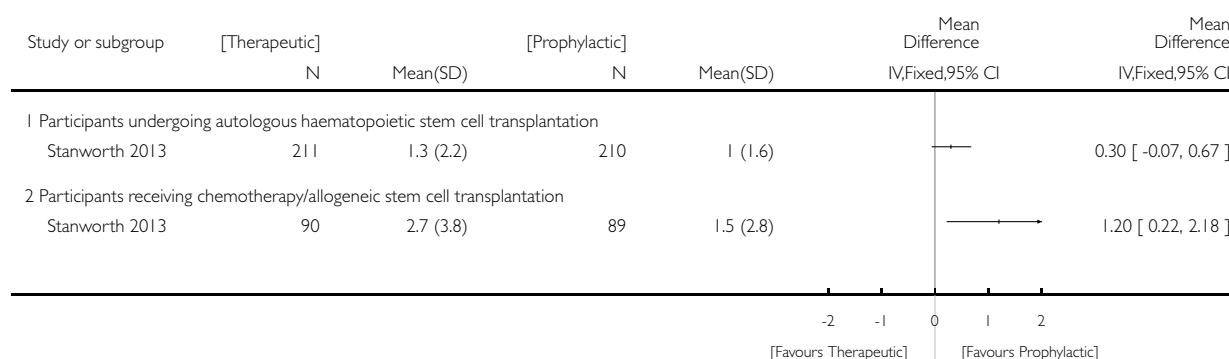


Analysis 1.16. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 16 Number of days with significant bleeding per patient per treatment category.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 16 Number of days with significant bleeding per patient per treatment category

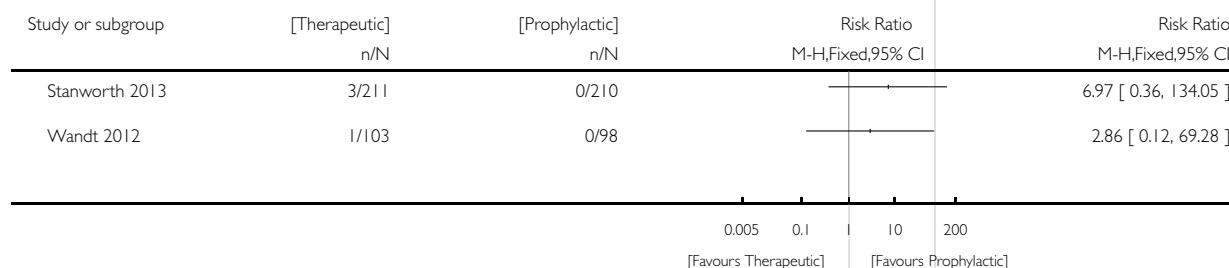


Analysis 1.17. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 17 Number of participants with severe or life threatening bleeding receiving autologous haematopoietic stem cell transplantation.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 17 Number of participants with severe or life threatening bleeding receiving autologous haematopoietic stem cell transplantation

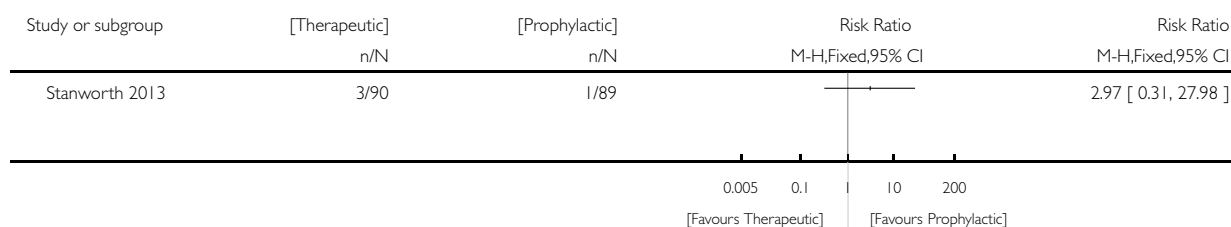


Analysis 1.18. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 18 Number of participants with severe or life threatening bleeding receiving chemotherapy/allogeneic haematopoietic stem cell transplantation.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 18 Number of participants with severe or life threatening bleeding receiving chemotherapy/allogeneic haematopoietic stem cell transplantation

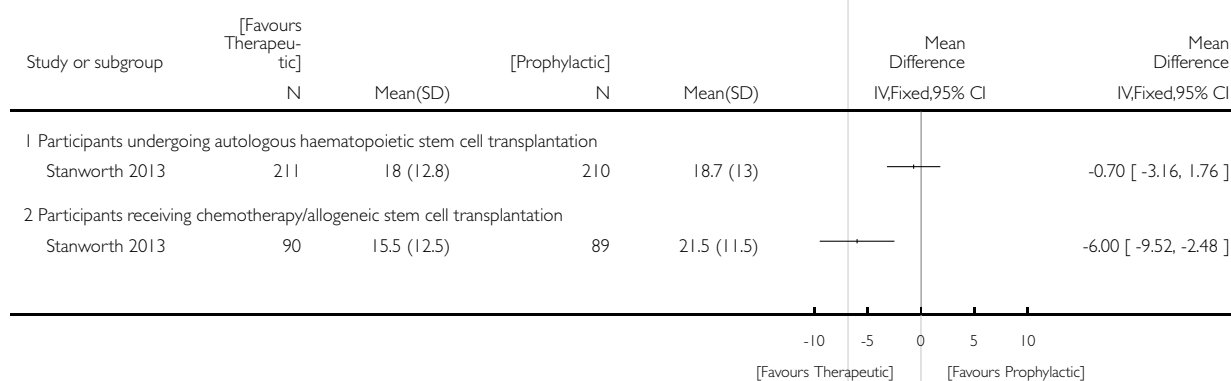


Analysis 1.19. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 19 Time to first bleeding event per treatment category.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 19 Time to first bleeding event per treatment category

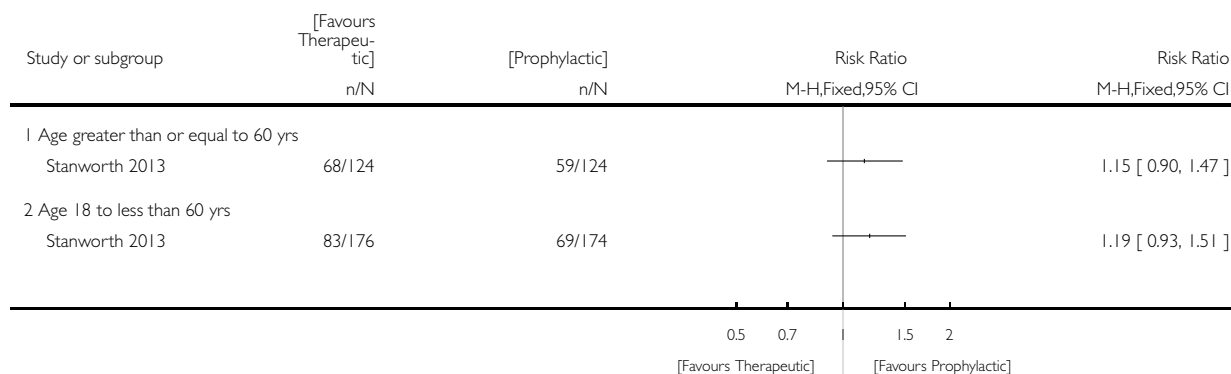


Analysis 1.20. Comparison 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion, Outcome 20 Number of participants with at least one bleeding episode per age category.

Review: A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation

Comparison: 1 Therapeutic or non-prophylactic platelet transfusion versus prophylactic platelet transfusion

Outcome: 20 Number of participants with at least one bleeding episode per age category



ADDITIONAL TABLES

Table 1. Therapeutic versus prophylactic platelet transfusion studies - characteristics of studies

Study	Characteristics of participants	Number of participants	Intervention	Duration of study	Type of platelet product	Primary outcome
Short-term follow-up (up to 30 days)						
Stanworth 2013	Adults with a haematological malignancy receiving myelosuppressive chemotherapy or undergoing autologous HSCT	600	Plt transfusions were not given if the plt count was $< 10 \times 10^9/L$ vs plt transfusions were given at a threshold plt count of $< 10 \times 10^9/L$	Median days on study was 30 days	Apheresis and pooled plt products	Occurrence of a WHO Grade 2 bleed or above
Wandt 2012	Adults with AML or undergoing autologous HSCT for leukaemia in re-	396	Plt transfusions were only given for WHO Grade 2 bleeds or higher	When plt count was self sustaining at more than $20 \times 10^9/L$ for 2 days, or a maxi-	Apheresis and pooled plt products	Number of plt transfusions during standardised observation period of 14 days

Table 1. Therapeutic versus prophylactic platelet transfusion studies - characteristics of studies (Continued)

	mis- sion, non-Hod- kin lymphoma, Hod- kin's disease, or myeloma		vs plt transfu- sions were given at a threshold plt count of $< 10 \times 10^9/L$	mum of 30 days, or at hospital dis- charge, or treat- ment failure, death or at study withdrawal, whichever occurred first		
Intermediate length follow-up (30 to 90 days)						
Grossman 1980	Patients with amegakaryocytic thrombocytope- nia	100	Plt transfusion given for clinically sig- nificant bleeding and just prior to invasive proce- dures vs prophy- lactic plt transfu- sion given if plt count $< 20 \times 10^9/L$	Mean days on study was 42 days (defined as plt count $< 50 \times 10^9/L$)	Equally given single-donor and random-donor plts	Not reported
Long-term follow-up (> 90 days)						
Murphy 1982	Children with acute leukaemia	56	Plt transfusion give in presence of 5 clinical in- dicators of bleed- ing vs prophy- lactic plt transfu- sion given if plt count $< 20 \times 10^9/L$	Bleeding outcomes and plt transfusion re- quirements were reported at 10 months Mean follow-up of 19.9 months to 20.4 months	Random-donor plts	Survival
Follow-up period not reported						
Sintnicolaas 1982	People with acute leukaemia	12	Plt transfusion given in pres- ence of haem- orrhage vs pro- phylactic platelet transfusion if plt count $< 20 \times 10^9/L$	Not reported	Single-donor plts	Not reported
Solomon 1978	Adults with AML	31	Plt transfusion given if clinically significant bleed-	Not reported	Random-donor plts	Not reported

Table 1. Therapeutic versus prophylactic platelet transfusion studies - characteristics of studies (Continued)

			ing or > 50% fall in plts to < 20 x 10 ⁹ /L in previous 24 hours vs prophylactic plt transfusion if plt count < 20 x 10 ⁹ /L			
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AML: acute myeloid leukaemia

H SCT: haematopoietic stem cell transplantation

plt: platelet

Table 2. Method of bleeding assessment and grading

Study	Bleeding primary outcome of study	Method of bleeding assessment reported	Clinically significant bleeding definition	Bleeding severity scale used	RBC usage part of bleeding severity assessment	RBC transfusion policy
Short-term follow-up (up to 30 days)						
Stanworth 2013	Yes	Yes	WHO Grade 2 or higher	Modified WHO	Yes	In the absence of bleeding a Hb < 90 g/L
Wandt 2012	No	Yes	WHO Grade 2 or higher	Modified WHO	Yes	To maintain a Hb > 80 g/L
Intermediate-length follow-up (30 to 90 days)						
Grossman 1980	No	Yes	Mild and severe bleeds. Mild bleeds not requiring active intervention	Study specific	No	Not reported
Long-term follow-up (> 90 days)						
Murphy 1982	No	No	Not defined	Study specific	No	Not reported
Follow-up period not reported						
Sintnicolaas 1982	No	No	Not defined	No	No	Not reported
Solomon 1978	No	No	Not defined	No	No	Not reported

Hb: haemoglobin
RBC: red blood cell

Table 3. Clinically significant bleeding event/participant

Study	Therapeutic-only platelet transfusion			Prophylactic platelet transfusion			Statistical analysis	P value
	Total number of participants	Number of participants	Percentage	Total number of participants	Number of participants	Percentage		
Short-term follow-up (up to 30 days)								
Stanworth 2013	300	151	50%	298	128	43%	Adjusted difference in proportions 8.4% (90% CI 1.7, 15)	0.06
Wandt 2012 ^a	197 (301 treatment cycles)	127	42% (36, 48) reported per treatment cycle	194 (343 treatment cycles)	65	19% (14, 23) reported per treatment cycle	42% vs 19%	< 0.0001
Intermediate-length follow-up (30 to 90 days)								
Grossman 1980 ^b	51	44	86%	49	30	61%	RR 1.01 (0.86, 1.18)	< 0.01
Long-term follow-up (> 90 days)								
Murphy 1982 ^c	21	11	52%	35	4	11%	RR 4.58 (1.67, 12.56)	Not reported
Murphy 1982 ^d	21	11	52%	35	10	29%	RR 1.83 (0.94, 3.56)	Not reported

CI: confidence interval

RR: risk ratio

^a In [Wandt 2012](#), bleeding was reported per treatment cycle. Participants were followed until either the platelet count was self sustaining at $20 \times 10^9/L$ or higher for 2 days, a maximum of 30 days, at hospital discharge, when treatment failure occurred, at death or at study withdrawal, whichever occurred first. Only participants receiving autologous haematopoietic stem cell transplantation received one treatment cycle, and therefore the number of participants was equal to the number of treatment cycles. Participants receiving chemotherapy could have received up to seven cycles of treatment.

^b Bleeding events in [Grossman 1980](#) were not reported over this review's predefined outcome period of 30 days. Participants were followed throughout their initial hospital stay and all subsequent admissions. Days on study was defined as a platelet count less than $50 \times 10^9/L$, and the mean length of follow-up was 41.6 days in the therapeutic-only group and 42.7 days in the prophylactic group.

^c Bleeding events in [Murphy 1982](#) were not reported over this review's predefined outcome period of 30 days. [Murphy 1982](#) reported bleeding outcome over the first 10 months of the study.

^d Bleeding events in [Murphy 1982](#) were also reported from study enrolment until study closure. The mean number of months observed varied from 19.9 months in the prophylactic group to 20.4 months in the therapeutic group.

Table 4. Total number of days on which significant bleeding event occurred per participant

Study	Therapeutic-only platelet transfusion		Prophylactic platelet transfusion		Comparison statistics	P value
	Number of participants	Days of clinically significant bleeding	Number of participants	Days of clinically significant bleeding		
Short-term follow-up (up to 30 days)						
Stanworth 2013	301	Mean 1.7 +/- 2.9 (SD) days per participant	299	Mean 1.2 +/- 2.0 (SD) days per participant	Rate ratio 1.52 (1.14, 2.03)	0.004
Long-term follow-up (> 90 days)						
Murphy 1982 ^a	21	40	35	15	Not reported	Not reported
Murphy 1982 ^b	21	46	35	68	Not reported	Not reported

SD: standard deviation

^a Bleeding events in [Murphy 1982](#) were not reported over this review's predefined outcome period of 30 days. [Murphy 1982](#) reported bleeding outcome over the first 10 months of the study.

^b Bleeding events in [Murphy 1982](#) were also reported from study enrolment until study closure. The mean number of months observed varied from 19.9 months in the prophylactic group to 20.4 months in the therapeutic group.

Table 5. Number of participants with at least one episode of severe or life-threatening bleeding

Study	Intervention	Total number of participants	Total number of participants with severe bleeding			Statistics used	P value
Short-term follow-up (up to 30 days)			WHO Grade 3	WHO Grade 4	WHO Grade 3 + 4		
Stanworth 2013	Therapeutic	301	4	2	6	WHO Grade 3 and 4	0.13

Table 5. Number of participants with at least one episode of severe or life-threatening bleeding (Continued)

						Odds ratio 6.05 (0.73, 279.72)		
	Prophylactic	299	1	0	1			
Intermediate-length follow-up (30 to 90 days)			Total number of participantswith severe bleeding			Statistics used	P value	
Grossman 1980 ^a	Therapeutic	51	44			Not reported	< 0.01	
	Prophylactic	49	30					
Study	Interven- tion	Total num- ber of par- ticipants	Total number of participants with severe bleeding per treatment cycle					
Short-term follow-up (up to 30 days)			WHO Grade 3	Statistics used	P value	WHO Grade 4	Statistics used	P value
Wandt 2012 ^b	Therapeutic	197 (301 treatment cycles)	7	Not reported	0.21	14	Not reported	0.0159
	Prophylactic	194 (343 treatment cycles)	3			4		

^a Bleeding events in Grossman 1980 were not reported over this review's predefined outcome period of 30 days. Participants were followed throughout their initial hospital stay and all subsequent admissions. Days on study was defined as a platelet count < 50 x 10⁹/L, and the mean length of follow-up was 41.6 days in the therapeutic-only group and 42.7 days in the prophylactic group.

^b In Wandt 2012, bleeding was reported per treatment cycle. Participants were followed until either the platelet count was self sustaining at 20 x 10⁹/L or higher for 2 days, a maximum of 30 days, at hospital discharge, when treatment failure occurred, at death or at study withdrawal, whichever occurred first. Only participants receiving autologous haematopoietic stem cell transplantation received one treatment cycle, and therefore the number of participants was equal to the number of treatment cycles. Participants receiving chemotherapy could have received up to seven cycles of treatment.

Table 6. Mortality

Study	Intervention	Participants	Mortality as per study definition	Study follow-up definitions	Mortality within 30 days			Mortality within 90 days
						Due to bleeding	Due to infection	
			Due to bleeding					All cause/ due to bleeding/ due to in-

Table 6. Mortality (Continued)

									fection
Short-term follow-up (up to 30 days)									
Stanworth 2013	Therapeutic	301	5	0	30 days	5	0	4	Not reported
	Prophylactic	299	4	0		4	0	3	
Wandt 2012	Therapeutic	197	5	2	Study follow-up was when plt count was self sustaining at more than 20 x 10 ⁹ /L for 2 days, or a maximum of 30 days, or at hospital discharge, or treatment failure, death or at study withdrawal, whichever occurred first. Participants receiving chemotherapy could have received up to 7 cycles of treatment	Not reported			Not reported
	Prophylactic	194	5	0					
Mortality reported within 1 month/course of chemotherapy									
Solomon 1978	Therapeutic	12	2	0	Mortality reported within 1 month/	0	0	Not reported	Not reported

Table 6. Mortality (Continued)

					course of chemo- therapy				
	Prophylac- tic	17	3	2		0	0	Not reported	
Intermediate-length follow-up (30 to 90 days)									
Grossman 1980	Therapeu- tic	51	Not reported	10	Mean days on study was 42 days (defined as plt count < 50 x 10 ⁹ / L). This of- ten included more than 1 period of thrombo- cytopenia per partici- pant Bacterial or fungal sepsis (or both) was a contribut- ing factor in 8 of the deaths 11 of the 14 haem- orrhagic deaths were in partici- pants who had plt al- loantibod- ies	Not reported			Not reported
	Prophylac- tic	49		4					
Long-term follow-up (> 90 days)									
Murphy 1982	Therapeu- tic	21	7	2	Mean fol- low-up 20. 4 months	Not reported			Not reported

Table 6. Mortality (Continued)

	Prophylactic	35	12	1	Mean follow-up 19.9 months				
Follow-up period not reported									
Sintnicolaas 1982	Therapeutic	Not reported	Not reported	0	Study follow-up not reported	Not reported			Not reported
	Prophylactic	Not reported		0					

plt: platelet

Table 7. Number of platelet transfusions or units

Study	Intervention	Number of participants in each arm	Platelet dose/transfusion	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)									
Stanworth 2013	Therapeutic	301	1 adult unit	1.7 +/- 2.6 (SD)	Rate ratio 0.62 (0.51, 0.74)	< 0.001	1.9 +/- 3.3 (SD)	Rate ratio 0.67 (0.55, 0.82)	< 0.001
	Prophylactic	299		3.0 +/- 3.2 (SD)			3.2 +/- 3.6 (SD)		
Wandt 2012 ^a	Therapeutic	197	1 platelet unit	1.63 (1.4, 1.83)	33.5% reduction in platelet transfusion (22.2, 43.1)	< 0.0001	Not reported	Not reported	Not reported
	Prophylactic	194		2.44 (2.2, 2.67)			Not reported	Not reported	
Intermediate-length follow-up (30 to 90 days)									
Grossman 1980 ^b	Therapeutic	51	Random-donor unit comprised	7.0	Not reported	< 0.01	Not reported		

Table 7. Number of platelet transfusions or units (Continued)

			a mean of 6.8 platelet concentrates, with an average yield of 0.8×10^{11} plts/unit. Single-donor unit had a mean of 4.8×10^{11} plts/collection	10.6					
	Prophylactic	49							
Long-term follow-up (> 90 days)									
Murphy 1982 ^c	Therapeutic	21	4 units/m ²	1.0	Not reported	Not reported	4.8/participant ^d	Not reported	Not reported
	Prophylactic	35		2.2			8.1/participant ^d		
Follow-up period not reported									
Sintnicolaas 1982	Number in each arm not reported		4×10^{11} plts/transfusion	Not reported			Not reported		
Solomon 1978	Therapeutic	12	Not reported	Not reported			Not reported		
	Prophylactic	19							
Study	Intervention	Number of participants in each arm	Platelet dose/transfusion	Number of platelet transfusions/course of chemotherapy	Comparison statistics	P value	Number of platelet units transfused/course of chemotherapy	Comparison statistics	P value
Solomon 1978	Therapeutic	12	Not reported	Not reported			16.1 +/- 3.4 (SD)	MD -15.8 (-19.2, -12.4)	Not reported

Table 7. Number of platelet transfusions or units (Continued)

	Prophylactic	19					31.9 +/- 5.9 (SD)		
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MD: mean difference

SD: standard deviation

^a In Wandt 2012, the analysis was adjusted for the stratification variables age (< 50 years and ≥ 50 years) and sex, and a random effect for repeated measures data of a participant's treatment cycles clustered in centres.

^b Platelet transfusions in Grossman 1980 were not reported over this review's predefined outcome period of 30 days. Participants were followed throughout their initial hospital stay and all subsequent admissions. Days on study was defined as a platelet count < 50 x 10⁹/L, and the mean length of follow-up was 41.6 days in the therapeutic-only group and 42.7 days in the prophylactic group.

^c Platelet transfusions in Murphy 1982 were reported over a 10-month period.

^d Not specified whether this value is a mean or a median (no further information available - author has died)

Table 8. Number of red cell transfusions per participant

Study	Intervention	Number of participants in each arm	Number of red cell transfusions/ participant	Comparison statistics	P value	Number of red cell units/ participant	Comparison statistics	P value
Short-term follow-up (up to 30 days)								
Stanworth 2013	Therapeutic	301	Mean 1.5 +/- 1.8 (SD)	Rate ratio 1.14 (0.96, 1.34)	0.13	Mean 3.0 +/- 3.4 (SD)	Rate Ratio 1.24 (1.04, 1.47)	0.02
	Prophylactic	299	Mean 1.5 +/- 1.7 (SD)			Mean 2.8 +/- 3.1 (SD)	MD 0.20 (-0.32, 0.72)	
Wandt 2012	Therapeutic	197	Mean 3.14 (2.81, 3.46)	Not reported	0.18	Not reported		
	Prophylactic	194	Mean 2.85 (2.58, 3.12)					
Intermediate-length follow-up (30 to 90 days)								
Grossman 1980 ^a	Therapeutic	25	15.8	Not reported	Not reported	Not reported		
	Prophylactic	25	9.8					
Long-term follow-up (> 90 days)								
Murphy 1982	Therapeutic	21	Not reported			Not reported		

Table 8. Number of red cell transfusions per participant (Continued)

	Prophylactic	35						
Follow-up period not reported								
Sintnico-laas 1982	Number in each arm not reported							
Solomon 1978	Therapeutic	12	Not reported			Not reported		
	Prophylactic	19						
Study	Intervention	Number of participants in each arm	Number of red cell transfusions/course of treatment	Comparison statistics	P value	Number of red cell units/course of treatment	Comparison statistics	P value
Solomon 1978	Therapeutic	12	Not reported			7.3 +/- 1.0 (SE)	MD -0.6 (-1.34, 0.14)	Not reported
	Prophylactic	19				6.7 +/- 1.0 (SE)		

MD: mean difference

SD: standard deviation

SE: standard error

^a Red cell transfusions in [Grossman 1980](#) were not reported over this review's predefined outcome period of 30 days. Participants were followed throughout their initial hospital stay and all subsequent admissions. Days on study was defined as a platelet count < 50 x 10⁹/L, and the mean length of follow-up was 41.6 days in the therapeutic-only group and 42.7 days in the prophylactic group.

Table 9. Platelet refractoriness

Study	Intervention	Participants	Platelet refractoriness	Definition of platelet refractoriness	Duration of study
Intermediate-length follow-up (30 to 90 days)					
Grossman 1980	Therapeutic	51	26	Corrected count increment of < 10 x 10 ⁹ /L following 2 or more consecutive transfusions in the absence of fever, disseminated intravascular coagulopathy, splenomegaly, or sepsis	Mean days on study was 42 days (defined as plt count < 50 x 10 ⁹ /L). This often included more than 1 period of thrombocytopenia per participant

Table 9. Platelet refractoriness (Continued)

	Prophylactic	49	27			
Long-term follow-up (> 90 days)						
Murphy 1982	Therapeutic	21	1	Bleeding for more than 4 days in which thrombocytopenia persists in the face of repeated platelet transfusions	Mean follow-up 20.4 months	
	Prophylactic	35	5		Mean follow-up 19.9 months	
Follow-up period not reported						
Sintnicolaas 1982	Therapeutic	Not reported	1	Not reported	Not reported	
	Prophylactic	Not reported	1			

Table 10. Subgroup analyses for disease and treatment category

		Overall	Acute leukaemia	Lymphoma or myeloma	CML or other cancer	Autologous stem cell transplant	Chemotherapy	Allogeneic stem cell transplant
Number of participants with at least 1 clinically significant bleeding episode ¹	Number of studies	2	1	1	1	2	1	1
	Number of participants	799	116	453	29	621	97	81
	Relative effect (95% CI)	Not estimable ²	RR 1.64 (1.11, 2.44)	RR 1.07 (0.88, 1.31)	RR 1.07 (0.50, 2.28)	Not estimable ³	RR 1.55 (1.05, 2.28)	RR 1.50 (0.86, 2.61)
		Overall	Acute leukaemia	Lymphoma or myeloma	CML or other cancer	Autologous stem cell transplant	Chemotherapy/Allogeneic stem cell transplant	
Total number of days on which bleeding occurred per participant ¹	Number of studies	1	Not reported	Not reported	Not reported	1	1	
	Number of participants	599	Not reported	Not reported	Not reported	420	179	

Table 10. Subgroup analyses for disease and treatment category (Continued)

	Participants						
	Relative effect (95% CI)	Rate ratio 1.52 (1.14, 2.03)	Not reported	Not reported	Not reported	MD 0.30 (-0.07, 0.67)	MD 1.20 (0.22, 2.18)
Number of participants with at least 1 episode of severe or life-threatening bleeding¹	Number of studies	2	Not reported	Not reported	Not reported	2	1
	Number of participants	801	Not reported	Not reported	Not reported	621	179
	Relative effect (95% CI)	RR 4.91 (0.86, 28.12)	Not reported	Not reported	Not reported	RR 4.89 (0.58, 41.41)	RR 2.97 (0.31, 27.98)
Time to first bleeding episode¹	Number of studies	2	Not reported	Not reported	Not reported	1	1
	Number of participants	801	Not reported	Not reported	Not reported	420	179
	Relative effect (95% CI)	Not estimable ⁴	Not reported	Not reported	Not reported	MD -0.70 (-3.16, 1.76)	MD -6.00 (-9.52, -2.48)

CI: confidence interval

CML: chronic myelogenous leukemia

MD: mean difference

RR: risk ratio

¹ Follow-up: median 30 days. Length of follow-up in the primary study contributing to this outcome was 30 days. Bleeding assessed using modified WHO grading scale.

² A meta-analysis of the data from [Stanworth 2013](#) and [Wandt 2012](#) was not performed due to the significant statistical heterogeneity seen. The observed statistical heterogeneity may relate to the different methods used in studies in the assessment and grading of bleeding ([Characteristics of included studies](#)). In [Wandt 2012](#), a therapeutic-only transfusion policy was associated with increased risk of bleeding events per treatment cycle when compared with a prophylaxis policy (RR 3.45, 95% CI 1.66 to 7.17). In [Stanworth 2013](#), the 95% CI crossed 1.0 (RR 1.17, 95% CI 0.99 to 1.39).

³ A meta-analysis of the data from [Stanworth 2013](#) and [Wandt 2012](#) was not performed due to the significant statistical heterogeneity seen. The observed statistical heterogeneity may relate to the different methods used in studies in the assessment and grading of bleeding ([Characteristics of included studies](#)). In [Stanworth 2013](#), there was no statistically significant difference in the number of clinically significant bleeding episodes between a therapeutic-only or prophylactic platelet transfusion policy (RR 1.04, 95% CI 0.85 to 1.28). However, in [Wandt 2012](#) there was a statistically significant difference (RR 3.45, 95% CI 1.66 to 7.17).

⁴ A meta-analysis of the data from [Stanworth 2013](#) and [Wandt 2012](#) was not performed due to the significant statistical heterogeneity seen. The observed statistical heterogeneity may relate to the different methods used in studies in the assessment and grading of bleeding ([Characteristics of included studies](#)). In [Stanworth 2013](#), the time to onset of significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (hazard ratio 1.30, 95% CI 1.03 to 1.64). In [Wandt 2012](#), the time to onset of significant bleeding was shorter in the therapeutic-only group than in the prophylaxis group (hazard ratio 2.61, 95% CI 1.84 to 3.72).

APPENDICES

Appendix I. CENTRAL (Cochrane Library) search strategy November 2011 to July 2015

- #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: [Hematologic Diseases] this term only
- #16 MeSH descriptor: [Leukemia] explode all trees
- #17 MeSH descriptor: [Lymphoma] explode all trees
- #18 MeSH descriptor: [Neoplasms, Plasma Cell] explode all trees
- #19 MeSH descriptor: [Anemia, Aplastic] explode all trees
- #20 MeSH descriptor: [Bone Marrow Diseases] explode all trees
- #21 MeSH descriptor: [Thrombocytopenia] explode all trees
- #22 (thrombocytopeni* or thrombocytopaeni* or leukemi* or leukaemi* or lymphom* or aplast* anemi* or aplast* anaemi* or myelodysplas* or myeloproliferat* or myelom* or plasm*ytom*)
- #23 (lymphogranulomato* or histiocy* or granulom* or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom*)
- #24 (burkitt* next (lymph* or tumo?r)) or lymphosarcom* or brill-symmer* or sezary
- #25 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) near/3 (malignan* or oncolog* or cancer* or neoplasm* or carcinoma*))
- #26 MeSH descriptor: [Antineoplastic Agents] explode all trees
- #27 MeSH descriptor: [Remission Induction] explode all trees
- #28 MeSH descriptor: [Antineoplastic Protocols] explode all trees
- #29 MeSH descriptor: [Stem Cell Transplantation] explode all trees
- #30 MeSH descriptor: [Bone Marrow Transplantation] this term only
- #31 MeSH descriptor: [Radiotherapy] explode all trees
- #32 MeSH descriptor: [Lymphatic Irradiation] this term only
- #33 (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow near/2 (transplant* or graft* or engraft* or rescu*)))
- #34 ((haematolog* or hematolog* or hemato-oncolog* or haemato-oncolog*) near/2 patients)
- #35 (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT)
- #36 (malignan* or oncolog* or cancer*):ti
- #37 #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 or #30 or #31 or #32 or #33 or #34 or #35 or #36
- #38 #13 and #37

Appendix 2. MEDLINE (OvidSP) search strategy November 2011 to July 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/
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 utilization)).tw.
13. or/7-12
14. exp Hematologic Neoplasms/ or Hematologic Diseases/
15. exp Leukemia/ or exp Lymphoma/
16. exp Neoplasms, Plasma Cell/
17. exp Anemia, Aplastic/
18. exp Bone Marrow Diseases/
19. exp Thrombocytopenia/
20. (thrombocytopeni* or thrombocytopaeni* or leukemi* or leukaemi* or lymphom* or aplast* anemi* or aplast* anaemi* or myelodysplas* or myeloproliferat* or myelom* or plasm??ytom*).tw,kf,ot.
21. (lymphogranulomato* or histiocy* or granulom* or thrombocythem* or thrombocythaemi* or polycythem* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom*).tw,kf,ot.
22. (burkitt* adj (lymph* or tumor?r)) or lymphosarcom* or brill-symmer* or sezaury).tw,kf,ot.
23. ((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* or carcinoma*)).tw,kf,ot
24. exp Antineoplastic Agents/ or exp Remission Induction/ or exp Antineoplastic Protocols/
25. exp Stem Cell Transplantation/ or Bone Marrow Transplantation/ or exp Radiotherapy/ or Lymphatic Irradiation/
26. (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow adj2 (transplant* or graft* or engraft* or rescu*))).tw,kf,ot.
27. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw,kf,ot.
28. (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw,kf,ot.
29. (malignan* or oncolog* or cancer*).ti.
30. or/14-29
31. 13 and 30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomi*.tw.
35. placebo.ab.
36. clinical trials as topic.sh.
37. randomly.ab.
38. groups.ab.
39. trial.ti.
40. or/32-39
41. exp animals/ not humans/
42. 40 not 41
43. 31 and 42

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 (thrombocyt* OR leukemia* OR leukaemia* OR lymphoma* OR aplastic anemia OR aplastic anaemia OR myelodysplas* OR myeloproliferat* OR multiple myeloma OR plasma cell myeloma OR plasmacytoma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR hodgkin* OR nonhodgkin*)
#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* OR carcinoma*))
#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] OR inprocess[sb]) NOT pubstatusnihms)
#9 #7 AND #8

Appendix 4. Embase (OvidSP) search strategy November 2011 to July 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/ or Hodgkin Disease/
17. Plasmacytoma/
18. exp Myeloproliferative Disorder/
19. exp Aplastic Anemia/
20. exp Thrombocytopenia/
21. (thrombocytopeni* or thrombocytopaeni* or leukemia* or leukaemia* or lymphom* or aplast* anemi* or aplast* anaemi* or myelodysplas* or myeloproliferat* or myelom* or plasm??ytom*).tw,kf,ot.
22. (lymphogranulomato* or histiocy* or granulom* or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom*).tw,kf,ot.
23. ((burkitt* adj (lymph* or tumor?r)) or lymphosarcom* or brill-symmer* or sezary).tw,kf,ot.
24. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm*)).tw,kf,ot.
25. exp Chemotherapy/
26. exp Stem Cell Transplantation/
27. exp Bone Marrow Transplantation/
28. exp Radiotherapy/

29. (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow adj2 (transplant* or graft* or engraft* or rescu*))).tw,kf,ot.
30. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw,kf,ot.
31. (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw,kf,ot.
32. (malignan* or oncolog* or cancer*).ti.
33. or/14-32
34. 13 and 33
35. Randomized Controlled Trial/
36. Randomization/
37. Single Blind Procedure/
38. Double Blind Procedure/
39. Crossover Procedure/
40. Placebo/
41. exp Clinical Trial/
42. Prospective Study/
43. (randomi* or double-blind* or single-blind* or RCT*).tw.
44. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
45. (crossover* or cross over* or cross-over* or placebo*).tw.
46. ((treble or triple) adj blind*).tw.
47. or/35-46
48. Case Study/
49. case report*.tw.
50. (note or editorial).pt.
51. or/48-50
52. 47 not 51
53. (animal* or cat or cats or dog or dogs or pig or pigs or sheep or rabbit* or mouse or mice or rat or rats or feline or canine or porcine or ovine or murine or model*).ti.
54. 52 not 53
55. 34 and 54
56. limit 55 to embase

Appendix 5. CINAHL (EBSCOhost) search strategy November 2011 to July 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*)
- S12 ((platelet* or thrombocyte*) N5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation))
- S13 S7 OR S8 OR S9 OR S10 OR S11 OR S12
- S14 (MH "Hematologic Neoplasms+")
- S15 (MH "Hematologic Diseases")
- S16 (MH Leukemia+)
- S17 (MH Lymphoma+)
- S18 (MH "Plasmacytoma+")

S19 (MH "Anemia, Aplastic+")
 S20 (MH "Bone Marrow Diseases+")
 S21 (MH Thrombocytopenia+)
 S22 (thrombocytopeni* or thrombocytopaeni* or leukemia* or leukaemi* or lymphom* or aplast* anemi* or aplast* anaemi* or myelodysplas* or myeloproliferat* or myelom* or plasm*?ytom*)
 S23 (lymphogranulomato* or histiocy* or granulom* or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom*)
 S24 (burkitt* lymph* or burkitt* tumo?r or lymphosarcom* or brill-symmer* or sezary)
 S25 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) N3 (malignan* or oncolog* or cancer* or neoplas* or carcinoma*))
 S26 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) N3 (malignan* or oncolog* or cancer* or neoplas* or carcinoma*))
 S27 (MH "Antineoplastic Agents+")
 S28 (MH "Hematopoietic Stem Cell Transplantation")
 S29 (MH "Bone Marrow Transplantation")
 S30 (MH Radiotherapy+)
 S31 (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow N2 (transplant* or graft* or engraft* or rescu*)))
 S32 ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) N2 patients)
 s33 (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT)
 S34 TI (malignan* or oncolog* or cancer*)
 S35 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 OR S30 OR S31 OR S32 OR S33 OR S34
 S36 S13 and S35
 S37 (MH CLINICAL TRIALS+)
 S38 PT Clinical Trial
 S39 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
 S40 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))
 S41 TI randomi* OR AB randomi*
 S42 MH RANDOM ASSIGNMENT
 S43 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
 S44 TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))
 S45 MH PLACEBOS
 S46 MH QUANTITATIVE STUDIES
 S47 TI placebo* OR AB placebo*
 S48 S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47
 S49 S36 AND S48

Appendix 6. Transfusion Evidence Library search strategy

Clinical Specialty: Haematology and Oncology AND Subject Area: Blood Components/Platelets
OR

All fields: (haematology OR haematological OR hematology OR hematological OR malignancy OR malignancies OR leukemia OR leukaemia OR lymphoma OR hodgkin OR hodgkins OR nonhodgkin OR aplastic OR thrombocytopenia OR thrombocytopenic OR myeloma OR plasmacytoma OR myelodysplasia) AND title:(platelet OR platelets OR thrombocyte OR thrombocytes) OR keywords: (platelet transfusion)

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

Topic: (platelet*) AND Topic: (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 Topic: (thrombocytop* OR leukemia* OR leukaemi* OR lymphoma* OR aplastic OR myelodysplas* OR myeloproliferat* OR myeloma OR plasmacytoma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR hodgkin* OR haematological OR hematological)) AND Topic: (systematic* OR random* OR blind* OR trial* OR control*)

Appendix 8. LILACS search strategy

((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 leukemia* OR leukaemi* OR lymphoma* OR aplastic OR myelodysplas* OR myeloproliferat* OR myeloma OR plasmacytoma 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

(platelet OR platelets OR thrombocyte OR thrombocytes OR thrombocytopheresis OR plateletpheresis) AND (thrombocytopenia OR thrombocytopenic OR leukemia OR leukaemia OR lymphoma OR aplastic OR myelodysplasia OR myeloproliferative OR myeloma OR plasmacytoma OR thrombocythemia OR thrombocythaemia OR polycythaemia OR Hodgkin OR haematological OR hematological) AND (randomized OR randomised OR randomly OR blind OR blinded OR trial OR control group)

Appendix 10. KoreaMed & PakMediNet search strategy

platelet*[ALL] AND “Randomized Controlled Trial” [PT]
thrombocyt*[ALL] AND “Randomized Controlled Trial” [PT]

Appendix 11. ClinicalTrials.gov & WHO ICTRP search strategy

Search Terms/Title: randomized OR randomised

Conditions: hematological neoplasm OR hematological malignancies OR leukemia OR lymphoma OR thrombocytopenia OR multiple myeloma OR aplastic anemia OR thrombocythemia OR polycythemia OR myelofibrosis OR hodgkin OR nonhodgkin OR plasmacytoma

Intervention: platelets OR platelet transfusion

Appendix 12. ISRCTN & EU Clinical Trials Register search strategy

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

Appendix 13. Hong Kong Clinical Trials Register search strategy

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)

#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
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	New search performed. New citation identified (Grossman 1980) from the electronic search of the Transfusion Evidence Library
7 March 2014	New citation required and conclusions have changed	The update review (version 2) (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). Two new outcomes have been added to the protocol (Estcourt 2014d) (platelet transfusion interval and quality of life) The primary and secondary outcomes have been reported over time frames prespecified within the protocol (Estcourt 2014d)

CONTRIBUTIONS OF AUTHORS

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

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

Erica Wood: protocol development and content expert.

Mariarena Trivella: protocol development and statistical expert.

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

Simon Stanworth: protocol development and content expert.

DECLARATIONS OF INTEREST

Gemma Crighton: none declared.

Lise Estcourt: author of one of the studies.

Erica Wood: author and chief investigator of one of the studies.

Mariarena Trivella: none declared.

Carolyn Doree: none declared.

Simon Stanworth: author and chief investigator of one of the studies.

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External sources

- No sources of support supplied

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 were no changes between the protocol for this review, [Estcourt 2014d](#), and the completed review.

Postprotocol changes to the review

The assessment of protocol deviation was not prespecified in the Methods section, however it was reviewed in the Risk of bias in included studies section and reported in the text. We added an additional query to the protocol to assess whether protocol deviation was balanced between treatment arms.

We did not prespecify in the protocol how we would deal with multi-arm studies. One study, [Grossman 1980](#), was a factorial RCT and included four arms: 1) therapeutic (T)/blood bank (BB)/random-donor platelets, 2) T/single donor (SD), 3) prophylactic (P)/BB, and 4) P/SD. The author provided aggregate data comparing the therapeutic and prophylactic for our study outcomes of interest.

We did not prespecify in the protocol how we would deal with any unit of analysis issues. In one study, [Wandt 2012](#), there were unit of analysis issues for the study's secondary outcomes. Some outcomes were reported per treatment cycle rather than per participant, and some participants received more than one cycle of chemotherapy. We resolved this by only using data within meta-analyses for participants who had received only one cycle of treatment (autologous HSCT participants). We have requested data from the author so that we can include data on all participants within a subsequent review. The study's primary outcome was adjusted for repeated courses of chemotherapy by the study authors ([Wandt 2012](#)).

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](#)).

Secondary outcomes: No study reported all-cause mortality within 90 days from the start of the study, overall survival within 90 days, overall survival within 180 days from the start of the study, quality of life, or platelet transfusion interval.

Subgroup analyses: We did not perform one of the four prespecified subgroup analyses, presence of fever, due to lack of data.

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.

We did not perform assessment of heterogeneity between studies due to the lack of standardised reporting of outcomes.

Sensitivity analyses: None of the six included trials had more than 20% of participants lost to follow-up, and all of the trials had some threats to validity, therefore neither pre-planned sensitivity analysis was performed.

NOTES

The previous review, [Estcourt 2012a](#), has now been split into four separate reviews.