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

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This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 3

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[Intervention Protocol]

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Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 3, 2014.

Citation: Estcourt LJ, Stanworth S, Doree C, Trivella M, Hopewell S, Murphy MF, Tinmouth A. Comparison of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD010983. DOI: 10.1002/14651858.CD010983.

ABSTRACT

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

To determine whether different platelet transfusion thresholds for administration of prophylactic platelet transfusions (platelet transfusions given to prevent bleeding) affect the efficacy and safety of prophylactic platelet transfusions in preventing bleeding in patients with haematological disorders after chemotherapy with or without stem cell transplantation.

BACKGROUND

Description of the condition

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

2009a; Rysler 2010; Stanworth 2013; Wandt 2012).

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

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

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

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

Description of the intervention

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

Prophylactic platelet transfusion threshold

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

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

How the intervention might work

Prophylactic platelet threshold

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

The routine use of platelet transfusions from the 1970s in patients with haematological malignancies resulted in a decreased mortality rate due to bleeding (less than 1% of patients) (Slichter 1980). Despite the lack of evidence, the widespread use of a threshold platelet count of 20×10^9/L for prophylactic platelet transfusions led to a marked growth in demand for platelet concentrates (Sullivan 2002). This increased demand stimulated research to address whether the threshold could be safely lowered to 10×10^9/L (Rebulla 1997, reviewed in Stanworth 2004). The consensus formulated from these trials was that patients should receive a

platelet transfusion when the platelet count is <10 x 10^9/L, unless there are other risk factors for bleeding, such as sepsis, concurrent use of antibiotics or other abnormalities of haemostasis (Board 2009; BCSH 2003; BCSH 2004; NBA 2012; Schiffer 2001; Slichter 2007; Tinmouth 2007) when the threshold should be raised.

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

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

Assessment of bleeding

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

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

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

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

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

Why it is important to do this review

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

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

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

This review will focus solely on the second question: which threshold should be used to trigger the transfusion of prophylactic platelets?

The other two questions will be assessed by 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 haematology patients will have significant logistical and financial implications for national health services as well as decreasing patients' exposure to the risks of transfusion. This knowledge is perhaps even more important in the development of platelet transfusion strategies in the developing world, where access to blood components is much more limited (Verma 2009).

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 blood group identical and ABO non-identical platelet transfusions. This is because these topics have been covered by recent systematic reviews (Butler 2013; Heddle 2008; Pavenski 2013; Shehata 2009).

OBJECTIVES

To determine whether different platelet transfusion thresholds for administration of prophylactic platelet transfusions (platelet transfusions given to prevent bleeding) affect the efficacy and safety

of prophylactic platelet transfusions in preventing bleeding in patients with haematological disorders after chemotherapy with or without stem cell transplantation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) in this review. There will be no restrictions on language or publication status.

Types of participants

Patients with haematological disorders receiving treatment with myelosuppressive chemotherapy and/or stem cell transplantation. We will include people of all ages, and we will include both inpatients and outpatients. If trials consist of mixed populations of patients, e.g. patients with diagnoses of solid tumours, only data from the haematological subgroups will be used. If subgroup data for haematological patients are not provided (after contacting the authors of the trial), the trial will be excluded if fewer than 80% of participants have a haematological disorder. Any patients that are not being treated with intensive chemotherapy or a stem cell transplant will be excluded. We will include patients with non-malignant haematological disorders (e.g. aplastic anaemia, congenital bone marrow failure syndromes) that are being treated with an allogeneic stem cell transplant.

Types of interventions

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

- Lower platelet count threshold (5 x 10^9/L) versus standard platelet transfusion threshold (10x10^9/L)
- Higher platelet count threshold (20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) versus standard platelet transfusion threshold (10 x 10^9/L)
- Different platelet count thresholds (5 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, or 50 x 10^9/L) that do not include a comparison against the standard platelet transfusion threshold (10 x 10^9/L)
- Alternative thresholds to guide prophylactic platelet transfusions (e.g. platelet mass, immature platelet fraction, absolute immature platelet number). There are currently no standard thresholds used for these alternative platelet measures, we will therefore use the study's own thresholds for these alternative measures.

Types of outcome measures

Primary outcomes

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

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

Secondary outcomes

- Mortality (all-causes, secondary to bleeding, and secondary to infection) within 30 days and 90 days from the start of the study.
- Number of platelet transfusions per patient and number of platelet components per patient within 30 days from the start of the study.
- Number of red cell transfusions per patient and number of red cell components per patient within 30 days from the start of the study.
- Platelet transfusion interval within 30 days from the start of the study.
- Proportion of patients requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate).
- Overall survival within 30 days, 90 days, and 180 days from the start of the study.
- Proportion of patients achieving complete remission within 30 days and 90 days from the start of the study.
- Total time in hospital within 30 days from the start of the study.
- Adverse effects of treatments (transfusion reactions, thromboembolism, transfusion-transmitted infection, development of platelet antibodies, development of platelet refractoriness) within 30 days from the start of the study.
- Quality of life, as defined by the individual studies.

We will express all primary and secondary outcomes in the formats defined in the Measures of treatment effect section of this protocol if data are available. Two of our outcomes are of special note as we expect them to be only narrative reports. Firstly, assessment of quality of life will use the study's own measure as there is no

definitive patient-reported outcome measure for this patient group (Estcourt 2013b). Secondly, the platelet transfusion interval can be calculated in many different ways and it is unlikely that the exact methodology will be reported sufficiently to allow us to combine the data.

Search methods for identification of studies

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

Electronic searches

Bibliographic databases

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

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

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

Databases of ongoing trials

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

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

Searching other resources

Handsearching of reference lists

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

Personal contacts

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

Data collection and analysis

Selection of studies

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

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

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

Data extraction and management

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

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

General information

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

Trial details

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

Characteristics of participants

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

Interventions

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

Assessment of bias

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

Outcomes measured

Number and severity of bleeding episodes. Mortality (all causes), and mortality due to bleeding. Disease-free survival. Proportion of patients 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 patients requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate). Quality of life. Adverse effects of treatments (e.g. transfusion reactions, thromboembolism, transfusion-transmitted infection, development of platelet antibodies or platelet refractoriness).

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

Assessment of risk of bias in included studies

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

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

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

Measures of treatment effect

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

For continuous outcomes, the mean and standard deviations will be recorded. For continuous outcomes measured using the same

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

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

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

Dealing with missing data

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

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

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

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

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

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

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

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

Subgroup analysis and investigation of heterogeneity

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

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

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

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

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

Sensitivity analysis

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

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

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

ACKNOWLEDGEMENTS

We thank the editorial base of the Cochrane Haematological Malignancies Review Group.

We thank the study authors who provided unpublished data or who kindly searched for data but they were no longer available: B Diedrich; K Heckman; P Rebulla; M Zumberg.

We thank the authors on the previous review (Stanworth 2004): S Brunskill; N Heddle; C Hyde; P Rebulla.

REFERENCES

Additional references

Ajani 1990
Ajani JA, Welsh SR, Raber MN. Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Investigation* 1990;**8**:141–53.

BCSH 2003
British Committee for Standards in Haematology (BCSH). Guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003;**122**:10–23.

BCSH 2004
British Committee for Standards in Haematology (BCSH). Transfusion guidelines for neonates and older children. *British Journal of Haematology* 2004;**124**(4):433–53.

Benson 2009
Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. *British Journal of Haematology* 2009;**147**(4):431–43.

Beutler 1993
Beutler E. Platelet transfusions: the 20,000/μL trigger. *Blood* 1993;**81**:1411–3.

Blajchman 2008
Blajchman MA, Slichter SJ, Heddle NM, Murphy MF. New strategies for the optimal use of platelet transfusions. *Hematology (American Society of Hematology Education Program)* 2008;**2008**(1):198–204.

Blumberg 2009
Blumberg N, Spinelli SL, Francis CW, Taubman MB, Phipps RP. The platelet as an immune cell - CD40 ligand and transfusion immune modulation. *Immunology Research* 2009;**45**:251–60.

Board 2009
The Board of the German Medical Association on the Recommendation of the Scientific Advisory Board. Platelet concentrates. Cross-sectional guidelines for therapy with blood components and plasma derivatives. *Transfusion Medicine and Hemotherapy* 2009;**36**:372–82.

Bolton-Maggs 2012
Bolton-Maggs PHB (Ed) and H Cohen on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2011 Annual SHOT Report*. Serious Hazards of Transfusion (SHOT), 2012.

Burnett 2011
Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al.Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *Journal of Clinical Oncology* 2011;**29**(4):369–77.

Butler 2013
Butler C, Doree C, Estcourt LJ, Trivella M, Hopewell S, Brunskill, SJ, et al.Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD009072]

Cameron 2007
Cameron B, Rock G, Olberg B, Neurath D. Evaluation of platelet transfusion triggers in a tertiary-care hospital. *Transfusion* 2007;**47**(2):206–11.

Cancer Research UK 2013
Cancer Research UK. Percentage change in European age-standardised three year average incidence rates, males, UK, 1991-2001 and 2008-2010. Cancer Research UK statistics at http://www.cancerresearchuk.org/cancer-info/cancerstats/ [Accessed 14/02/2013].

CDC 2012
CDC (Center for Disease Control). United States Cancer Statistics. National Program of Cancer Registries (NPCR) 2012:[Accessed 14/02/2013].

Coleman 2004
Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al.Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer* 2004;**90**(7):1367–73.

Cook 2004
Cook RJ, Heddle NM, Rebulla P, Sigouin CS, Webert KE. Methods for the analysis of bleeding outcomes in randomized trials of platelet transfusion triggers. *Transfusion* 2004;**44**:1135–42.

De la Serna 2008
De la Serna J, Montesinos P, Vellenga E, Rayon C, Parody R, Leon A, et al.Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. *Blood* 2008;**111**(7):3395–402.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Duke 1910
Duke WW. The relation of blood platelets to hemorrhagic disease. Description of a method for determining the bleeding time and coagulation time and report of 3 cases of hemorrhagic disease relieved by transfusion. *Journal of the American Medical Association* 1910;**55**:1185–92.

Estcourt 2011
Estcourt LJ, Stanworth SJ, Murphy MF. Platelet transfusions for patients with haematological malignancies: who needs them?. *British Journal of Haematology* 2011;**154**(4):425–40.

Estcourt 2012b
Estcourt LJ, Birchall J, Lowe D, Grant-Casey J, Rowley M, Murphy MF. Platelet transfusions in haematology patients: are we using them appropriately?. *Vox Sanguinis* 2012;**103**(4):284–93.

Estcourt 2013a
Estcourt LJ, Heddle N, Kaufman RM, McCullough J, Murphy MF, Slichter S, et al. On behalf of the BEST (Biomedical Excellence for Safer Transfusion) Collaborative. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. *Transfusion* 2013;**53**(7):1531–43.

Estcourt 2013b
Estcourt LJ, Pinchon D, Symington E, Kelly AM, Doree C, Brunskill S, et al.Does bleeding affect patient reported outcome measures in patients with myelodysplasia or hematologic malignancies: a systematic review. *Transfusion* 2013;**[Early on-line publication]**. [DOI: 10.1111/trf.12441]

Fielding 2007
Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al.Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood* 2007;**109**(3):944–50. [PUBMED: 17032921]

Gaydos 1962
Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukaemia. *New England Journal of Medicine* 1962;**266**:905–9.

Gerday 2009
Gerday E, Baer VL, Lambert DK, Pau DA, Sola-Visner MC, Pysher TJ, et al.Testing platelet mass versus platelet count to guide platelet transfusions in the neonatal intensive care unit. *Transfusion* 2009;**49**:2034–9.

Gmür 1991
Gmür J, Burger J, Schanz U, Fehr J, Schaffner A. Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia. *Lancet* 1991;**338**:1223–6.

Gratwohl 2010
Gratwohl A, Baldomero H, Aljurf M, Pasquini MC, Bouzas LF, Yoshimi A, et al.Hematopoietic stem cell transplantation: a global perspective. *JAMA* 2010;**303**(16):1617–24.

Greeno 2007
Greeno E, McCullough J, Weisdorf D. Platelet utilisation and the transfusion trigger: a prospective analysis. *Transfusion* 2007;**72**(2):201–5.

Harrison 2001
Harrison P, Ault KA, Chapman S, Charie L, Davis B, Fujimoto K, et al.An interlaboratory study of a candidate reference method for platelet counting. *American Journal of Clinical Pathology* 2001;**115**:448–59.

Heddle 2003
Heddle NM, Cook RJ, Webert KE, Sigouin C, Rebulla P. Methodologic issues in the use of bleeding as an outcome in transfusion medicine studies. *Transfusion* 2003;**43**:742–52.

Heddle 2008
Heddle, NM, Arnold, DM, Boye, D, Webert, KE, Resz, I, Dumont, LJ. Comparing the efficacy and safety of apheresis and whole blood-derived platelet transfusions: a systematic review. *Transfusion* 2008;**48**(7):1447–58.

Heddle 2009a
Heddle NM, Cook RJ, Tinmouth A, Kouroukis CT, Hervig T, Klapper E, et al.A randomized controlled trial comparing standard and low dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood* 2009;**113**(7):1564–73.

Heddle 2009b
Heddle NM, Webbert K. Investigation of acute transfusion reactions. In: Murphy MF, Pamphilion DH editor(s). *Practical Transfusion Medicine*. 4th Edition. Blackwell, 2009:63–89.

Higby 1974
Higby DJ, Cohen E, Holland JF, Sinks L. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. *Transfusion* 1974;**14**:440–5.

Higgins 2011a
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in Statistics. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Knowles 2011
Knowles S (Ed), Cohen H, on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2010 Annual SHOT Report*. Serious Hazards of Transfusion (SHOT), 2011.

Koreth 2004
Koreth R, Weinert C, Weisdorf DJ, Key NS. Measurement of bleeding severity: a critical review. *Transfusion* 2004;**44**: 605–17.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Murphy 1982
Murphy S, Litwin S, Herring LM, Koch P, Remischovky J, Donaldson MH, et al.Indications for platelet transfusion in children with acute leukemia. *American Journal of Hematology* 1982;**12**:347–56.

NBA 2012
National Blood Authority. *The National Blood Authority's Patient Blood Management Guideline: Module 3 - Medical*. National Blood Authority, 2012.

ONS 2012
ONS. Cancer incidence and mortality tables and charts. Office of National Statistics 2012, issue tcm77–259491: [Accessed 14/02/2013].

Parmar 1998
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Passweg 2012
Passweg JR, Baldomero H, Gratwohl A, Bregni M, Cesaro S, Dreger, P, et al.The EBMT activity survey: 1990-2010. *Bone Marrow Transplant* 2012;**47**(7):906–23.

Patel 2009
Patel B, Kirkland K, Szydlo R, Pearce R, Clark R, Craddock C, et al.Favorable outcomes with alemtuzumab-conditioned unrelated donor stem cell transplantation in adults with high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in first complete remission. *Haematologica* 2009;**94**:1399–406.

Pavenski 2013
Pavenski K, Rebulla P, Duquesnoy R, Saw CL, Slichter SJ, Tanael S, et al. International Collaboration for Guideline Development, Implementation. Evaluation for Transfusion Therapies, Collaborators. Efficacy of HLA-matched platelet transfusions for patients with hypoproliferative thrombocytopenia: a systematic review. *Transfusion* 2013; **Epub**:ahead of print. [DOI: 10.1111/trf.12175]

Pearce 2011
Pearce S, Rowe GP, Field SP. Screening of platelet for bacterial contamination at the Welsh Blood Service. *Transfusion Medicine* 2011;**21**(1):25–32.

Pendry 2011
Pendry K, Davies T. An audit of use and wastage in the north west of England and North Wales: where have all the platelets gone?. *Blood and Transplant Matters* 2011;**34**: 17–9.

Popovsky 1985
Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985;**25**:573–7.

Rachet 2009
Rachet B, Maringe C, Nur U, Quaresma M, Shah A, Woods LM, et al.Population-based cancer survival trends in England and Wales up to 2007: an assessment of the NHS cancer plan for England. *The Lancet Oncology* 10;**4**:351–69.

Rebulla 1997
Rebulla P, Finazzi G, Marangoni F, Avvisati G, Gugliotta L, Tognoni G, et al.The threshold for prophylactic platelet transfusions in adults with acute myeloid leukaemia. *New England Journal of Medicine* 1997;**337**:1870–5.

Review Manager 2012
The Nordic Cochrane Centre. Review Manager (RevMan). 5.2. Copenhagen: The Cochrane Collaboration, 2012.

Rysler 2010
Rysler C, Stoffel N, Buser A, Gratwohl A, Tsakiris DA, Stern M. Effect of beta-blockers, Ca2+antagonists, and benzodiazepines on bleeding incidence in patients with chemotherapy induced thrombocytopenia. *Platelets* 2010; **21**(1):77–83.

Schiffer 2001
Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al.Platelet transfusion for patients with

cancer: clinical practice guidelines of the American Society of Clinical Oncology. *Journal of Clinical Oncology* 2001;**19**: 1519–38.

Schünemann 2011
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Segal 2005
Segal HC, Briggs C, Kunka S, Casbard A, Harrison P, Machin SJ, et al.Accuracy of platelet counting haematology analysers in severe thrombocytopenia and potential impact on platelet transfusion. *British Journal of Haematology* 2005; **128**:520–5.

Shehata 2009
Shehata, N, Tinmouth, A, Naglie, G, Freedman, J, Wilson, K. ABO-identical versus non-identical platelet transfusion: a systematic review. *Transfusion* 2009;**49**:2442–53.

Silliman 2003
Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L, et al.Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003;**101**(2):454–62.

Slichter 1978
Slichter SJ, Harker LA. Thrombocytopenia: mechanisms and management of defects in platelet production. *Clinical Haematology* 1978;**7**:523–39.

Slichter 1980
Slichter SJ. Controversies in platelet transfusion therapy. *Annual Reviews of Medicine* 1980;**31**:509–40.

Slichter 2005
Slichter SJ, Davis K, Enright H, Braine H, Gernsheimer T, Kao KJ, et al.Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. *Blood* 2005;**105**: 4106–14.

Slichter 2007
Slichter SJ. Evidence-based platelet transfusion guidelines. Hematology (American Society of Hematology Education Program) 2007:172–8.

Slichter 2010
Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al.Dose of prophylactic platelet transfusions and prevention of haemorrhage. *New England Journal of Medicine* 2010;**362**:600–13.

Solomon 1978
Solomon J, Bofenkamp T, Fahey JL, Chillar RK, Beutler E. Platelet prophylaxis in acute non-lymphoblastic leukemia. *The Lancet* 1978;**1 (8058)**:267.

Stanworth 2010
Stanworth SJ, Dyer C, Choo L, Bakrania L, Copplestone A, Llewelyn C, et al.Do all patients with hematologic malignancies and severe thrombocytopenia need prophylactic platelet transfusions? Background, rationale, and design of a clinical trial (trial of platelet prophylaxis) to assess the effectiveness of prophylactic platelet transfusions. *Transfusion Medicine Reviews* 2010;**24**(3):163–71.

Stanworth 2013
Stanworth SJ, Estcourt LJ, Powter G, Kahan B, Dyer C, Choo L, et al.A no-prophylaxis platelet transfusion strategy for hematologic cancers. *New England Journal of Medicine* 2013;**368**(19):1771–80. [PUBMED: WOS: 000318540000005]

Sterne 2011
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention.* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sullivan 2002
Sullivan MT, McCullough J, Schreiber GB, Wallace EL. Blood collection and transfusion in the United States in 1997. *Transfusion* 2002;**42**(10):1253–60.

Taylor 2010
Taylor C (Ed.), Cohen H, Mold D, Jones H, et al.on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2009 Annual SHOT Report*. SHOT Steering Group, 2010.

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; Vol. 8, issue 16. [DOI: 10.1186/1745-6215-8-16]

Tinmouth 2007
Tinmouth AT. Chapter 18: Platelet transfusion, alloimmunization and management of platelet refractoriness. *Canadian Blood Services.* 4th Edition. Canadian Blood Services, 2007.

TRAP 1997
TRAP Study Group. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. The Trial to Reduce Alloimmunization to Platelets Study Group. *New England Journal of Medicine* 1997;**337**(26):1861–9.

Verma 2009
Verma A, Agarwal P. Platelet utilization in the developing world: strategies to optimize platelet transfusion practices. *Transfusion and Apheresis Science* 2009;**41**(2):145–9.

Wandt 2012
Wandt H, Schaefer-Eckart K, Wendelin K, Pilz B, Wilhelm M, Thalheimer M, et al.Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* 2012;**380**(9850):1309–16.

Webert 2006
Webert KE, Cook RJ, Sigouin CS, Rebulla P, Heddle NM. The risk of bleeding in thrombocytopenic patients with acute myeloid leukaemia. *Haematologica* 2006;**91**(11): 1530–7.

WHO 1979
WHO. *WHO Handbook for Reporting Results of Cancer Treatment*. WHO Offset publication No. 48. Geneva: World Health Organisation, 1979.

References to other published versions of this review

Estcourt 2012a
Estcourt L, Stanworth SJ, Doree C, Hopewell S, Murphy MF, Tinmouth A, et al.Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database of Systematic Reviews* 2012, Issue 5. [DOI: 10.1002/14651858.CD004269.pub3]

Stanworth 2004
Stanworth SJ, Hyde C, Heddle N, Rebulla P, Brunskill S, Murphy MF. Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004269.pub2]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL (*The Cochrane Library*) 2013 search strategy

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

#26 MeSH descriptor: [Radiotherapy] explode all trees
#27 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)
#28 ((haematolog* or hematolog* or hemato-oncolog* or haemato-oncolog*) near/2 patients)
#29 (malignan* or oncolog* or cancer*):ti
#30 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 #13 and #30

Appendix 2. MEDLINE (Ovid) search strategy (Nov 2011-2013)

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 utili?ation)).tw.
13. or/7-12
14. exp Hematologic Neoplasms/
15. exp Leukemia/ or exp Lymphoma/
16. exp Multiple Myeloma/
17. exp Anemia, Aplastic/
18. exp Bone Marrow Diseases/
19. exp Thrombocytopenia/
20. (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
21. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm*)).tw.
22. exp Antineoplastic Agents/
23. exp Stem Cell Transplantation/ or Bone Marrow Transplantation/ or exp Radiotherapy/
24. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*).tw.
25. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw.
26. (malignan* or oncolog* or cancer*).ti.
27. or/14-26
28. 13 and 27

Appendix 3. PubMed search strategy (epublications only)

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

Appendix 4. EMBASE (Ovid) search strategy (Nov 2011-2013)

1. Thrombocyte/
2. (platelet* or thrombocyte*).ti.
3. 1 or 2
4. Blood Transfusion/
5. transfus*.ti.
6. 4 or 5
7. 3 and 6
8. Thrombocyte Transfusion/
9. Thrombocytopheresis/
10. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
11. (thrombocytopheres* or plateletpheres*).tw.
12. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
13. or/7-12
14. Hematologic Malignancy/
15. Lymphoma/
16. NonHodgkin Lymphoma/
17. Hodgkin Disease/
18. exp Myeloproliferative Disorder/
19. exp Aplastic Anemia/
20. exp Thrombocytopenia/
21. (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*).tw.
22. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm*)).tw.
23. exp Chemotherapy/
24. exp Stem Cell Transplantation/
25. exp Bone Marrow Transplantation/
26. exp Radiotherapy/
27. (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant* or rituximab).tw.
28. ((haematolog* or hematolog*) adj2 patients).tw.

29. (malignan* or oncolog* or cancer*).ti.
30. or/14-29
31. 13 and 30

Appendix 5. CINAHL (EBSCOhost) search strategy (Nov 2011-2013)

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 S8 OR S9 OR S10 OR S11 OR S12
S14 (MH "Hematologic Neoplasms+")
S15 (MH Leukemia+)
S16 (MH Lymphoma+)
S17 (MH "Multiple Myeloma+")
S18 (MH "Anemia, Aplastic+")
S19 (MH "Bone Marrow Diseases+")
S20 (MH Thrombocytopenia+)
S21 (thrombocytopeni* or thrombocytopaeni* or leukemia or leukaemia or lymphoma* or aplastic anemia or aplastic anaemia or myelodysplas* or myeloproliferat* or multiple myeloma or plasma cell myeloma or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin*)
S22 ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) N3 (malignan* or oncolog* or cancer* or neoplasm*))
S23 (MH "Antineoplastic Agents+")
S24 (MH "Hematopoietic Stem Cell Transplantation")
S25 (MH "Bone Marrow Transplantation")
S26 (MH Radiotherapy+)
S27 (chemotherap* or radiotherap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or bone marrow transplant*)
S28 ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) N2 patients)
S29 TI (malignan* or oncolog* or cancer*)
S30 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29
S31 S13 and S30

Appendix 6. TRANSFUSION EVIDENCE LIBRARY search strategy (2013)

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

Appendix 7. Web of Science (CPCI-S) search strategy (2013)

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

Appendix 8. LILACS search strategy (2013)

((platelet* AND (prophyla* OR transfus* OR products OR component* OR concentrate* OR apheres* OR pooled OR single donor OR random donor OR protocol* OR trigger* OR threshold*)) AND (thrombocytop* OR leukemi* OR leukaemi* OR lymphoma* OR aplastic OR myelodysplas* OR myeloproliferat* OR myeloma OR thrombocythemi* OR thrombocythaemi* OR polycythemi* OR polycythaemi* OR myelofibros* OR hodgkin* OR haematological OR hematological)) AND db:("LILACS") AND type_of_study:("clinical_trials" OR "systematic_reviews")

Appendix 9. INDMED search strategy (2013)

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

Appendix 10. KoreaMed & PakMediNet search strategy (2013)

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

Appendix 11. ClinicalTrials.gov & ICTRP search strategy (2013)

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

Appendix 12. ISRCTN & EU Clinical Trials Register search strategy (2013)

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

Appendix 13. Hong Kong Clinical Trials Register search strategy (2013)

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

CONTRIBUTIONS OF AUTHORS

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

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

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

Marialena Trivella: protocol development and statistical expert.

Sally Hopewell: protocol development and methodological expert.

Mike Murphy: protocol development and content expert.

Alan Tinmouth: protocol development and content expert.

DECLARATIONS OF INTEREST

Lise Estcourt: none declared.

Simon Stanworth: none declared.

Carolyn Doree: none declared.

Marialena Trivella: none declared.

Sally Hopewell: none declared.

Mike Murphy: none declared.

Alan Tinmouth: none declared.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK.

To support the work of the Systematic Review Initiative (SRI)

External sources

- German Ministry of Education and Research (BMBF) towards support of the Cochrane Haematological Malignancies Group, Germany.

For their editorial support

NOTES

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