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Different doses of prophylactic platelet transfusion for preventing bleeding in patients with haematological disorders after chemotherapy or stem cell transplantation

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Abstract

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

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

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CONTRIBUTIONS OF AUTHORS

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Carolyn Doree: protocol development, searching and selection of studies.
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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: study author of platelet dose platelet transfusion trial.

NOTES

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

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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 (HSCTs) are carried out annually worldwide (Gratwohl 2010), and are used to treat both malignant and non-malignant haematological disorders. Autologous HSCT is the commonest type of HSCT (57% to 59%) (Gratwohl 2010; Passweg 2012). However, chemotherapy and stem cell transplantation can lead to prolonged periods of severe thrombocytopenia (De la Serna 2008; Heddle 2009a; Rysler 2010; Stanworth 2013; Wandt 2012).

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

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

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

lung injury; and immunomodulatory effects (Benson 2009; Blumberg 2009; Bolton-Maggs 2012; Heddle 2009b; Knowles 2011; Pearce 2011; Popovsky 1985; Silliman 2003; Knowles 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).

Dose of prophylactic platelet transfusions

The platelet dose is the number of platelets contained within a standard platelet transfusion. For adults, the usual dose given is a single apheresis unit or a pool of four to six whole blood-derived platelets, with the absolute number of platelets in the range of 300×10^9 to 600×10^9 (Stanworth 2005). The experimental interventions will be low dose or high dose platelet transfusion strategies. Low dose platelet transfusions will be platelet transfusions containing a similar dose to that given in the low dose arm of Slichter 2010 ($1.1 \times 10^{11}/m^2 \pm 25\%$). High dose platelet transfusions will be platelet transfusions containing a similar dose to that given in the high dose arm of Slichter 2010 ($4.4 \times 10^{11}/m^2 \pm 25\%$). If the exact dose is unknown the study's own definition of high or low dose will be used.

How the intervention might work

Optimal dose of prophylactic platelets—The dose of the platelet product transfused was based upon the perceived need to raise the patient's platelet count above a certain safe threshold. Over the years, our understanding of bleeding in thrombocytopenic patients has advanced and there is now evidence to suggest that patients require only approximately 7100 platelets/μL per day to maintain haemostasis (Hanson 1985). Platelets have been shown to provide an endothelial supportive function by plugging gaps in the endothelium of otherwise intact blood vessels. Animal studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells (Blajchman 1981; Kitchens 1975; Nachman 2008). This thinning and fenestration of the endothelium is accompanied by the ongoing and increased use of circulating platelets to prevent the loss of red blood cells (RBCs) through these gaps.

A mathematical model predicted that smaller, more frequent doses of platelets would be as effective as higher doses of platelets in maintaining patients' platelet counts above an agreed threshold (Hersh 1998). This raised the question of whether thrombocytopenic bleeding

could be prevented with a lower platelet dose (Tinmouth 2003). Such a strategy has potential economic and resource advantages, as fewer platelet transfusions might be required and donor exposures might be reduced.

Several studies have tried to address this question. The two largest studies came to different conclusions (Heddle 2009a; Slichter 2010). One trial was stopped early because of an excess of World Health Organization (WHO) grade 4 bleeding (Heddle 2009a), and the other study found no difference in bleeding between treatment arms (Slichter 2010).

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 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 at different doses.

Why it is important to do this review

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

- Firstly, what is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

- Secondly, which threshold should be used to trigger the transfusion of prophylactic platelets?
- Thirdly, are prophylactic platelet transfusions superior to therapeutic platelet transfusions for the prevention 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 first question; what is the optimal prophylactic platelet dose to prevent thrombocytopenic bleeding?

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

The previous version of this review showed that there was no difference in the number of patients who developed WHO grade 2 or above bleeding between patients who received a low dose, standard dose or high dose platelet transfusion strategy (Estcourt 2012a). However, it was not able to establish whether there was any difference in the number of days on which bleeding occurred or in the number of patients with severe or life-threatening haemorrhage (WHO grade 3 to 4) between the various platelet dose strategies. A new study has been published since the previous review (Lufa 2011).

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

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

OBJECTIVES

To determine whether different doses of prophylactic platelet transfusions (platelet transfusions given to prevent bleeding) affect their efficacy and safety 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). 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. We will exclude any patients who are not being treated with intensive chemotherapy or a stem cell transplant. Patients with non-malignant haematological disorders (e.g. aplastic anaemia, congenital bone marrow failure syndromes) who are being treated with an allogeneic stem cell transplant will be included.

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 the frequency of platelet transfusions, type of platelet component, or platelet count transfusion threshold, although we will take this information into account in the analysis where available.

We will include the following comparisons:

- Low dose versus standard dose platelet transfusions
- Low dose versus high dose platelet transfusions
- High dose versus standard dose platelet transfusions

Low dose platelet transfusions will be platelet transfusions containing a similar dose to that given in the low dose arm of Slichter 2010 ($1.1 \times 10^{11}/m^2 \pm 25\%$). Standard dose platelet transfusions will be platelet transfusions containing a similar dose to that given in the intermediate dose arm of Slichter 2010 ($2.2 \times 10^{11}/m^2 \pm 25\%$). If the exact dose is unknown the study's own definition of high or low dose will be used. High dose platelet transfusions will be platelet transfusions containing a similar dose to that given in the high dose arm of Slichter 2010 ($4.4 \times 10^{11}/m^2 \pm 25\%$). If the exact dose is unknown the study's own definition of high, standard or low dose will be used.

Types of outcome measures

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

- The number of patients with at least one bleeding episode.
- The total number of days on which bleeding occurred per patient.

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

Secondary outcomes

- Mortality (all-causes, secondary to bleeding, and secondary to infection) within 30 days and 90 days from the start of the study.
- Number of platelet transfusions per patient and number of platelet components per patient within 30 days from the start of the study.
- Number of red cell transfusions per patient and number of red cell units per patient within 30 days from the start of the study.
- Platelet transfusion interval within 30 days from the start of the study.
- Proportion of patients requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate) within 30 days from the start of the study.
- Overall survival within 30 days, 90 days, and 180 days from the start of the study.
- Proportion of patients achieving complete remission within 30 days and 90 days from the start of the study
- The 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 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).

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 lists 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.

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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 transfusion doses. 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. Adverse effects of treatments (e.g. transfusion reactions, thromboembolism, transfusion-transmitted infection, development of platelet antibodies or platelet refractoriness). Quality of life.

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

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

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

Two review authors 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 (includes assessment of blinding of participants, personnel and outcome assessors)?
- Were incomplete outcome data adequately addressed (for every outcome separately)?
- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias?

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

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% CIs, or the standardised mean difference (SMD) for outcomes measured using different scales. For time-to-event outcomes we will extract the hazard ratio (HR) from published data according to Parmar 1998 and Tierney 2007.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Appendix 1. CENTRAL (The Cochrane Library) 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

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#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/

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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

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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

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#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

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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

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