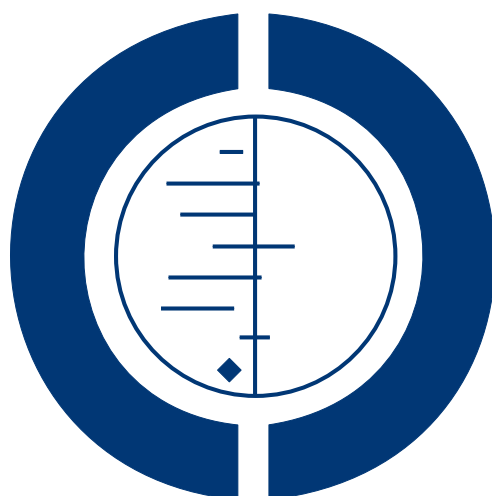


Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anaemia, and other congenital bone marrow failure disorders (Protocol)

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Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anaemia, and other congenital bone marrow failure disorders

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ABSTRACT

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

To assess the efficacy and safety of a restrictive versus liberal red cell transfusion strategy for patients with long-term bone marrow failure. These include myelodysplasia, acquired aplastic anaemia, and other inherited bone marrow failure disorders.

BACKGROUND

Please see [Published notes](#) for an explanation of some technical terms.

Description of the condition

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

Clinical symptoms of patients with bone marrow failure disorders are related to the underlying cytopenias (anaemia, neutropenia and thrombocytopenia) that arise from this ineffective haematopoiesis. Patients can present with fatigue and shortness of breath due to anaemia, recurrent infections due to neutropenia and bleeding or bruising due to thrombocytopenia. The chronic and often severe nature of the anaemia results in the majority of patients eventually requiring regular red cell transfusions if they cannot tolerate or are ineligible for curative therapy, or if they have refractory disease (disease not responsive to curative therapy) (Goldberg 2010; Young 2008).

Bone marrow failure disorders can be classified according to the underlying pathophysiology, into three broad categories: myelodysplastic syndromes (MDS), acquired aplastic anaemia, and inher-

ited bone marrow failure disorders.

MDS encompasses a diverse group of disorders that are characterised by dysplasia in one or more cell lines (blood cells have an abnormal shape or size), ineffective haematopoiesis, and an increased risk of developing acute myeloid leukaemia (AML). Overall the incidence of MDS is estimated at between 2.3 to 4.5 per 100,000 per year (Dinmohamed 2014; Ma 2007; Ma 2012; Neukirchen 2011). However, the incidence increases markedly with age, with the highest incidence in those aged over 80 years (> 30 per 100,000 per year) (Dinmohamed 2014; Ma 2007; Ma 2012; Neukirchen 2011). The International Prognostic Scoring System (IPSS) and the Revised IPSS (IPSS-R) are used to predict the prognosis of patients with MDS at diagnosis (Greenberg 2012). Management recommendations for patients with MDS have largely been based on their IPSS score (Killick 2014). 'Low-risk' MDS includes patients with IPSS Low/Intermediate-1 (INT-1), and 'high-risk' MDS includes those with IPSS Intermediate-2 (INT-2)/High (Killick 2014).

Acquired aplastic anaemia is a disease that results in a hypocellular bone marrow with quantitative defects of all three cell lines. The incidence in Europe and North America is two per million population per year (Issaragrisil 2006; Montané 2008), whereas the incidence in Asia is higher, with estimates ranging from 3.9 to 7.4 per million per year (Young 2008). The underlying cause is unknown in most cases, but certain industrial chemicals (Young 2008), agricultural pesticides (Issaragrisil 2006; Muir 2003), drugs (Issaragrisil 2006; Young 2008), and hepatitis viruses (Rauff 2011) have been reported to cause aplastic anaemia. Treatment is tailored to the individual needs of the patient, but involves a combination of supportive care for pancytopenia (red cell and platelet transfusions, prophylactic antimicrobials), immunosuppressive therapy, and bone marrow transplant.

Inherited bone marrow failure disorders include the 'classical' bone marrow failure disorders associated normally with a global haematopoietic defect (Fanconi anaemia), Dyskeratosis congenita, Shwachman-Diamond syndrome, Pearson syndrome, and familial aplastic anaemia (both X-linked and autosomal forms)), as well as those associated with a single lineage haematopoietic defect resulting in anaemia, the most common being Diamond-Blackfan anaemia (Dokal 2008). The most common of these, Fanconi anaemia, has a reported incidence of approximately one in 360,000 live births, with a carrier frequency of one in 300 (Giri 2004). Haematopoietic stem cell transplant forms the definitive treatment in many of these disorders, but supportive therapy in terms of red cell and platelet transfusions are often needed for symptomatic relief, either prior to transplant, or for those patients not suitable to undergo transplant.

Description of the intervention

Red cell transfusions play a central role in the supportive management of patients with long-term bone marrow failure disorders.

Currently, there are no clear national UK guidelines for the recommendation of a particular transfusion strategy, restrictive (giving a red cell transfusion if the haemoglobin (Hb) falls below a certain low threshold) or liberal (giving a red cell transfusion at a higher Hb threshold), for such patients.

The use of a restrictive transfusion policy is supported by the results of a recent systematic review of 19 randomised controlled trials (RCTs) (Carson 2012). This systematic review included RCTs of both medical and surgical patients of all ages (excluding neonates), but did not include patients with long-term bone marrow failure disorder. Carson 2012 showed that a restrictive transfusion strategy significantly reduced the risk of receiving a transfusion by 39% (risk ratio (RR) 0.61, 95% CI 0.52 to 0.72), without a negative impact on the rate of adverse events (including mortality, myocardial infarction, stroke, pneumonia and thromboembolism). The transfusional requirements and outcomes of the patients included within Carson 2012 may differ from patients with bone marrow failure disorders, and it is therefore less clear whether a restrictive strategy would be beneficial in patients with long-term cytopenias. Patients with bone marrow failure disorders often present with bi- or tri-lineage cytopenia. There is therefore some concern that concurrent anaemia with thrombocytopenia may increase the risk of bleeding (Valeri 2007). A pilot RCT (60 patients with acute leukaemia or receiving a haematopoietic stem cell transplantation (HSCT), studied the effects of haemoglobin concentration on bleeding risk. It compared those transfused at a haemoglobin threshold of less than 80 g/dL to those transfused at a haemoglobin trigger of less than 120 g/L (Webert 2008). This small feasibility study, (conducted to assess whether a larger definitive study would be possible) did not demonstrate a difference in clinically significant bleeding between the study arms, but this may be because the study was not designed to detect a difference. The planned larger definitive study has not yet been performed. The Webert 2008 RCT is included in an ongoing systematic review examining the transfusion needs of patients with haematological malignancies receiving intensive chemotherapy, with or without haematopoietic stem cell transplantation (Butler 2014).

How the intervention might work

A restrictive red cell transfusion for patients with chronic bone marrow failure, if feasible, may be advantageous for several reasons. Firstly, the risk of alloimmunisation (i.e., the production of antibodies in response to foreign antigens) to leucocytes in red cell transfusions due to the production of both human leukocyte antigen and non-human leukocyte antigen (minor histocompatibility) antibodies may be reduced with a more restrictive transfusion strategy. This may result in a lower risk of graft rejection for those patients with aplastic anaemia treated later with an allogeneic bone marrow transplant (Kaminski 1990). Secondly, regular red cell transfusion in the supportive treatment of low-risk MDS result in raised serum ferritin, which together with transfusion dependence,

act as independent adverse risk factors for survival in this group of patients (Malcovati 2005). Indeed, serum ferritin levels > 2500 µg/L are associated with an increased transplant-related mortality in those patients with high-risk MDS undergoing myeloablative stem cell transplant (Armand 2011). Thirdly, a restrictive transfusion strategy may also be beneficial when considering the risks of transfusion transmitted infections, which although are very low in the UK (as a result of robust screening programmes), is still a significant problem in those countries with particularly high rates of HIV transmission.

One further aspect to consider regarding the success of a restrictive versus liberal transfusion programme is the effect on the quality of life in this group of patients, data for which are limited. A prospective multicentre trial of 36 elderly low- and intermediate-risk MDS treated to a target haemoglobin of > 120 g/L with either erythropoietin (with the addition of Granulocyte-colony stimulating factor (G-CSF) if no response) or red cell transfusion showed an improvement in quality of life in terms of fatigue, dyspnoea, constipation and social functioning (Nilsson-Ehle 2011). Particularly in the older population, where aggressive treatment may be inappropriate, a more supportive approach with regular red cell transfusions, primarily for symptomatic relief, may be an attractive alternative for many people with chronic marrow failure disorders.

This forms the basis of this systematic review, which aims to compare the effects of a liberal versus restrictive red cell transfusion programme in those patients undergoing supportive, rather than active treatment for bone marrow failure, with a particular focus on its impact on quality of life.

Why it is important to do this review

Currently, no clear transfusion strategies are recommended in national guidelines for patients with bone marrow failure disorders (Anonymous 2009; Killick 2014; NBA 2012). As such, many patients are transfused following local hospital policies, or transfused according to individual patient circumstances, which may result in under- or over-transfusion. Studies of other patient groups, specifically those in critical care and those with acute upper gastrointestinal bleeding have shown possible improved outcomes in terms of survival within the restrictive transfusion arm (Hebert 1999; Villanueva 2013).

A restrictive transfusion policy with a lower haemoglobin threshold may be attractive for people who are regularly transfused for several reasons. Despite the very low risks of viral transmission of HIV, hepatitis B and C in the UK, such blood-borne viruses remain considerably higher in other parts of the world. In addition, less frequent red cell transfusions would also reduce the number of non-infective adverse events. In 2012, according to the UK Serious Hazards of Transfusion (SHOT) reporting system, haemolytic transfusion reactions were responsible for 19%, and transfusion-related circulatory overload (TACO) for 13% of all pathological

transfusion reactions (Bolton-Maggs 2013). Death or severe morbidity occurred in 43% of all cases of TACO reported to SHOT (Bolton-Maggs 2013). However, a transfusion policy that is too restrictive may leave the patient with harmful levels of anaemia, with potential adverse effects on myocardial remodelling and the subsequent development of cardiovascular disease (Pereira 2003). Therefore, a greater understanding of the safety and benefits of a liberal versus restrictive transfusion policy in patients with bone marrow failure disorders enables the provision of a more tailored red cell transfusion strategy for such patients.

OBJECTIVES

To assess the efficacy and safety of a restrictive versus liberal red cell transfusion strategy for patients with long-term bone marrow failure. These include myelodysplasia, acquired aplastic anaemia, and other inherited bone marrow failure disorders.

METHODS

Criteria for considering studies for this review

Types of studies

This review will include only randomised controlled trials (RCTs), irrespective of language or publication status.

Types of participants

We will include all patients with long-term bone marrow failure disorders that require allogeneic blood transfusion, who are not being actively treated with a haematopoietic stem cell transplant, or intensive chemotherapy. These disorders include myelodysplasia syndromes (MDS), acquired or inherited aplastic anaemia and other congenital bone marrow failure disorders. Due to the inherited nature of a number of bone marrow failure disorders, we will include patients of all ages, including neonates.

Types of interventions

We will include all allogeneic red cell transfusion strategies defined as 'restrictive' and 'liberal'. For individual studies, the restrictive intervention group will include those patients who receive an allogeneic red cell transfusion only below a definite 'trigger' or 'threshold' haemoglobin or haematocrit. The liberal control group would include those patients that receive an allogeneic red cell transfusion based on a more generous transfusion strategy, whereby transfusion usually occurs at a higher haemoglobin or haematocrit.

Types of outcome measures

We will categorise all outcomes according to short-, medium-, and long-term outcomes. We will report the exact definition of these time frames over time periods that are common to as many studies as possible (for example, up to 30 days, one to six months, and greater than six months).

Primary outcomes

- All-cause mortality
- Mortality due to bleeding, infection, transfusion reactions, or iron overload, or both.

Secondary outcomes

- Frequency and length of hospital admissions
- Frequency and length of intensive care admission
- Quality of life (measured using validated scales, for example, EQ-5D, FACT-AN, and EORTC-30)
- Non-fatal serious adverse events classified as:
 - serious bleeding (e.g. WHO/CTCAE (The Common Terminology Criteria for Adverse Events) grade 3 (or equivalent) or above);
 - adverse transfusion reactions (including, but not limited to transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), blood-group A, B or O incompatibility and transfusion transmitted infection (TTI));
 - iron overload (defined by ferritin > 1000 and/or clinical symptoms and/or signs of iron overload); and
 - serious infections (infections requiring admission to hospital).
- Blood product requirement
 - Red cell transfusion requirements (for example, number of units required or number of transfusion episodes) and intervals
 - Platelet transfusion requirements (for example, number of pools required, or number of transfusion episodes) and intervals
- Usage of iron chelation therapy

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) will formulate the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

We will search for RCTs in the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) ([Appendix 1](#))
- MEDLINE (1946 to present) ([Appendix 2](#))
- Embase (1974 to present) ([Appendix 3](#))
- CINAHL (1937 to present)
- PubMed (epublications only)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to present)
- LILACS (1980 to present)
- IndMed (1986 to present)
- PakMediNet (1995 to present)
- KoreaMed (1958 to present)
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to present)

We will search for ongoing RCTs in the following databases.

- ClinicalTrials.gov
- World Health Organization International Clinical Trials Registry Platform (ICTRP)

We will combine searches in MEDLINE with the Cochrane RCT highly sensitive search filter, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)). We will combine searches in Embase and CINAHL with the relevant SIGN RCT studies filter (www.sign.ac.uk/methodology/filters.html). We will not limit searches by year of publication, language or publication status.

Searching other resources

We will also perform handsearches of the reference lists of included studies in order to identify further relevant studies. We will make contact with lead authors of relevant studies to identify any unpublished material, missing data or information regarding ongoing studies.

Data collection and analysis

Selection of studies

We will select studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two authors (YG, LE) will independently screen all the remaining references for relevance against the full eligibility criteria. Full text articles will be retrieved for all references for which a decision on eligibility cannot be made from title and abstract alone. Study design features will be assessed against the inclusion criteria. Additional

information will be requested from study authors as necessary to assess the eligibility for inclusion of individual studies. The two authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, the decision of eligibility will be referred to a third author (PV). The results of study selection will be reported using a PRISMA flow diagram (Moher 2009).

Data extraction and management

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (YG, LE) will independently extract data onto standardised forms and perform a cross-check (Higgins 2011a). The data extraction form will be piloted on two included RCTs. The review authors will come to a consensus on the required changes. If an agreement cannot be reached, a third review author (PV) will be consulted. The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. The following information will be extracted for each study:

1. Source: Study identification (ID); report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details.
2. General study information: Publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed.
3. Study details and methods: Location; country; setting; number of centres; total study duration; recruitment dates; length of follow-up; power calculation; primary analysis (and definition); stopping rules; method of sequence generation; allocation concealment; blinding (of clinicians, participants and outcome assessors); any concerns regarding bias; inclusion and exclusion criteria; primary outcome(s); secondary outcomes.
4. Characteristics of interventions: Number of study arms; description of experimental arm; description of control arm; duration of red cell storage; frequency of minor blood-group A, B or O- mismatched transfusions; other treatments (for example, gamma irradiation of blood products).
5. Characteristics of participants: Age; gender; ethnicity; primary diagnosis; subgroup classification of primary disease type where appropriate (for example, World Health Organization (WHO) 2008 classification of MDS (Swerdlow 2008), severity of primary disease, where appropriate (for example, severe, very severe and non-severe aplastic anaemia (Bacigalupo 1988; Camitta 1975), prognostic classification of primary disease where appropriate (IPSS-R prognostic scoring system for MDS (Greenberg 2012); additional therapy received; risk of alloimmunisation; baseline haematology laboratory parameters; cofounders reported.
6. Participant flow: Total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for review

outcomes); number of allocated patients who received planned treatment; number of drop-outs with reasons (percentage in each arm); protocol violations; missing data.

7. Outcomes: All-cause mortality (undefined and within short-, medium- and long-term periods); mortality due to infection, bleeding, transfusion reactions or iron overload, or both; non-fatal serious adverse events (bleeding, adverse transfusion reactions, iron overload and serious infections); number and volume of red cell transfusion units received per patient; interval between red cell transfusions, number and volume of platelet doses received per patient; interval between platelet transfusion; frequency and duration of hospital admission, frequency and duration of intensive care admission; usage of iron chelation therapy; quality of life.

Assessment of risk of bias in included studies

We will assess the quality of all RCTs using the Cochrane 'Risk of bias' criteria, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (YG, LE) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. A brief description of the judgement statements upon which the authors have assessed potential bias will be reported in the characteristics of included studies table. A consensus on the degree of risk of bias will be met through comparison of the review authors statements and where necessary, through consultation with a third author (PV). We will use the 'Risk of bias' assessment to explore statistical heterogeneity in each included study and to perform sensitivity analyses. We will use the Cochrane Collaboration's tool for assessing risk of bias (low, high or unclear risk) in the following areas.

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

Measures of treatment effect

For continuous outcomes we will record the mean, standard deviation, and total number of participants in both the treatment and control groups. For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups.

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

We will analyse continuous outcomes using the same scale, using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we will present the standard mean difference (SMD). We will extract and

report hazard ratios (HRs) if available, for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose built method based on the Parmar and Tierney tool (Parmar 1998; Tierney 2007).

For dichotomous outcomes, we will report risk ratios (RRs) with a 95% CI (and for mortality, if HRs are not available). Where the number of observed events is small (< 5% of sample per group), we will use the Peto Odds Ratio (OR) method for analysis (Deeks 2011).

Where appropriate, we will report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with CIs.

If the data available cannot be reported in any of the formats described above, we will provide a descriptive summary of the available information.

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster-randomised trials, cross-over studies, and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

Where we identify data to be missing or unclear in published literature, we will contact study authors directly. We will record the number of patients lost to follow-up for each study. Where possible, we will analyse data by intention-to-treat (ITT) but if insufficient data are available, we will present per protocol (PP) analyses (Higgins 2011c).

Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity of treatment effects between studies using a χ^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if $I^2 > 50\%$, or considerable if $I^2 > 80\%$. We perceive that at least moderate clinical and methodological heterogeneity will be identified within the studies selected for inclusion; we will then use a random-effects model. If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where at least 10 studies are identified for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Lau 2006; Sterne 2011).

Data synthesis

We will perform analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into Review Manager 5 software (RevMan 2014). One review author (YG) will enter the data and a second author (LE) will then check for accuracy. Where meta-analysis is feasible, we will use the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and the inverse variance method for continuous outcomes. We will use the generic inverse variance method for time-to-event outcomes.

Summary of findings

We will use the GRADE system to build a 'Summary of findings' table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). The outcomes we will include (comparing a restrictive versus liberal transfusion strategy) are listed below.

1. All-cause mortality
2. Mortality secondary to bleeding/infection/transfusion reactions or iron overload
3. Quality of life
4. Frequency and length of hospital admissions
5. Serious bleeding (e.g. WHO/CTCAE grade 3 (or equivalent) or above)
6. Serious infections (requiring admission to hospital)
7. Red cell transfusion requirements

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity.

- Subgroup analysis for all bone marrow failure disorders
 - Type of bone marrow failure disorders (myelodysplastic syndromes (MDS), aplastic anaemia, congenital bone marrow failure disorder)
 - Paediatric (< 18 years) versus adult (18 to 65 years) versus elderly (> 65 years)
- Subgroup analysis for individual disorders
 - High-risk MDS versus low-risk MDS (as defined by IPSS-R prognostic risk categories/scores)

- Acquired aplastic anaemia versus inherited childhood bone marrow failure disorder

Sensitivity analysis

We will assess the robustness of our findings by performing the following sensitivity analyses where appropriate.

- Including only those studies with a 'low risk' of bias (for example, RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).
- Including only those studies with less than a 20% drop out rate.

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Bone Marrow Diseases] this term only
- #2 MeSH descriptor: [Myelodysplastic Syndromes] explode all trees
- #3 MeSH descriptor: [Anemia, Aplastic] explode all trees
- #4 MeSH descriptor: [Myelodysplastic-Myeloproliferative Diseases] explode all trees
- #5 MeSH descriptor: [Preleukemia] this term only
- #6 myelodysplas* or mielodispl*s* or MDS or preleukemi* or preleukaemi* or pre-leukemi* or pre-leukaemi* or dysmyelopoietic or dysmyelopoiesis or erythropen* or erythropan* or erythrocytopen* or erythrocytopaen* or paroxysmal nocturnal h*emoglobinuria or marchiafava micheli syndrome
- #7 ((refractor* or refrakt* or aplastic or dyserythropoietic) near/3 (anemi* or anaemi*))
- #8 RAEB* or RCMD* or RARS* or RAMD* or CDA* or RAEM*
- #9 (((unilineage or uni-lineage or multilineage or multi-lineage) near/3 dysplas*) or ringed sideroblasts)
- #10 5q-syndrome or del 5q or deletion 5q
- #11 ((refractor* or refrakt*) near/3 (thrombocytopen* or neutropen* or cytopeni* or cytopaeni* or zytopen*))
- #12 chronic myelomonocytic leuk*emia or CMML
- #13 (marrow near/3 (failure* or aplas* or dysplas* or hypoplas*))
- #14 (fanconi or dyskeratosis congenita or (shwachman near/2 diamond) or pearson syndrome or Diamond Blackfan)

#15 (smoldering* near/3 leuka*m*)
 #16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
 #17 MeSH descriptor: [Blood Transfusion] this term only
 #18 MeSH descriptor: [Blood Component Transfusion] explode all trees
 #19 MeSH descriptor: [Erythrocyte Transfusion] this term only
 #20 (erythrocyte* or "red blood cell*" or "red cell*" or blood or RBC*) near/5 (transfus* or unit*)
 #21 (transfus* or erythrocyte* or "red cell*" or "red blood cell*" or RBC*) near/5 (trigger* or level* or target* or threshold* or rule* or restrict* or liberal* or requir* or reduc* or limit* or support* or management or sparing or strategy*)
 #22 (blood near/3 (management or sparing or support* or strateg*))
 #23 hemotransfus* or haemotransfus* or hemotherap* or haemotherap*
 #24 ((erythrocyte* or blood) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or product* or component* or management or replac*)):ti
 #25 ("red cell*" or "red blood cell*" or RBC* or transfus*):ti
 #26 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
 #27 #16 and #26

Appendix 2. MEDLINE (Ovid) search strategy

1. BLOOD TRANSFUSION/
2. BLOOD COMPONENT TRANSFUSION/
3. ERYTHROCYTE TRANSFUSION/
4. ((erythrocyte* or red blood cell* or red cell* or blood or RBC*) adj5 (transfus* or unit*)):tw.
5. ((transfus* or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (trigger* or level* or threshold* or rule* or target* or restrict* or liberal* or requir* or reduc* or limit* or support* or management or sparing or strategy*)):tw.
6. (blood adj3 (management or sparing or support or strateg*)):tw.
7. ((erythrocyte* or blood) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or product* or component* or management or replac*)):ti.
8. (hemotransfus* or haemotransfus* or hemotherap* or haemotherap*):tw.
9. (red cell* or red blood cell* or RBC* or transfus*):ti.
10. or/1-9
11. Bone Marrow Diseases/
12. exp Myelodysplastic Syndromes/
13. exp Anemia, Aplastic/
14. exp Myelodysplastic-Myeloproliferative Diseases/
15. Preleukemia/
16. (myelodysplas* or mielodispl?s* or MDS or preleukemi* or preleukaemi* or pre-leukemi* or pre-leukaemi* or dysmyelopoietic or dysmyelopoiesis or erythropeni* or erythropani* or erythrocytopen* or erythrocytopaen* or paroxysmal nocturnal hemoglobinuria or paroxysmal nocturnal haemoglobinuria or marchiafava micheli syndrome).tw.
17. ((refractor* or refrakt* or aplastic or dyserythropoietic or sideroblasti*) adj3 (anemi* or anaemi*)):tw,kf,ot.
18. (RAEB* or RCMD* or RARS* or RAMD* or CDA* or RAEM*).tw,kf,ot.
19. (((unilineage or uni-lineage or multilineage or multi-lineage) adj3 dysplas*) or ringed sideroblasts).tw.
20. (5q-syndrome or del 5q or deletion 5q).tw.
21. ((refractor* or refrakt*) adj3 (thrombocytopen* or neutrop* or cytopeni* or cytopaeni* or zytopen*)):tw,kf,ot.
22. (chronic myelomonocytic leuk?emia or CMML).tw.
23. (marrow adj3 (failure* or aplas* or dysplas* or hypoplas*)):tw,kf,ot.
24. (fanconi or dyskeratosis congenita or (shwachman adj2 diamond) or pearson syndrome or Diamond Blackfan).tw.
25. (smoldering* adj3 leuka?m*).tw,kf,ot.
26. or/11-25
27. 10 and 26
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomi*.tw.

31. placebo.ab.
32. clinical trials as topic.sh.
33. randomly.ab.
34. trial.tw.
35. groups.ab.
36. or/28-35
37. exp animals/ not humans/
38. 36 not 37
39. 27 and 38

Appendix 3. Embase (Ovid) search strategy

1. *Blood Transfusion/
2. Blood Component Therapy/
3. Erythrocyte Transfusion/
4. ((erythrocyte* or red blood cell* or red cell* or blood or RBC*) adj5 (transfus* or unit*)).tw.
5. ((transfus* or erythrocyte* or red cell* or red blood cell* or RBC*) adj5 (trigger* or level* or threshold* or rule* or target* or restrict* or liberal* or requir* or reduc* or limit* or support* or management or sparing or strategy*)).tw.
6. (blood adj3 (management or sparing or support* or strateg*)).tw.
7. ((erythrocyte* or blood) and (use* or usage* or utiliz* or utilis* or requir* or need* or administ* or product* or component* or management or replac*)).ti.
8. (hemotransfus* or haemotransfus* or hemotherap* or haemotherap*).tw.
9. (transfus* or red cell* or red blood cell* or RBC*).ti.
10. or/1-9
11. Bone Marrow Disease/
12. Bone Marrow Aplasia/ or Bone Marrow Depression/ or Bone Marrow Hypoplasia/ or Bone Marrow Necrosis/ or Dyserythropoiesis/ or Erythropenia/ or Febrile Bone Marrow Aplasia/
13. exp Myelodysplastic Syndrome/
14. exp Aplastic Anemia/
15. Preleukemia/
16. exp Sideroblastic Anemia/
17. (myelodysplas* or mielodispl?sic* or MDS or preleukemi* or preleukaemi* or pre-leukemi* or pre-leukaemi* or dysmyelopoietic or dysmyelopoiesis or erythropeni* or erythropani* or erythrocytopen* or erythrocytopaen* or paroxysmal nocturnal hemoglobinuria or paroxysmal nocturnal haemoglobinuria or marchiafava micheli syndrome).tw.
18. ((refractor* or refrakt* or aplastic or dyserythropoietic or sideroblasti*) adj3 (anemi* or anaemi*)).tw,kf,ot.
19. (RAEB* or RCMD* or RARS* or RAMD* or CDA* or RAEM*).tw,kf,ot.
20. (((unilineage or uni-lineage or multilineage or multi-lineage) adj3 dysplas*) or ringed sideroblasts).tw.
21. (5q-syndrome or del 5q or deletion 5q).tw.
22. ((refractor* or refrakt*) adj3 (thrombocytopen* or neutrop* or cytopeni* or cytopaeni* or zytopen*)).tw,kf,ot.
23. (chronic myelomonocytic leuk?emia or CMML).tw.
24. (marrow adj3 (failure* or aplas* or dysplas* or hypoplas*)).tw,kf,ot.
25. (fanconi or dyskeratosis congenita or (shwachman adj2 diamond) or pearson syndrome or Diamond Blackfan).tw.
26. (smo?ldering* adj3 leuka?m*).tw,kf,ot.
27. or/11-26
28. 10 and 27
29. exp Clinical Trial/
30. Randomized Controlled Trial/
31. Randomization/
32. Single Blind Procedure/
33. Double Blind Procedure/
34. Crossover Procedure/
35. Placebo/

36. Prospective Study/
37. (randomi* or double-blind* or single-blind* or RCT*).tw.
38. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
39. (crossover* or cross over* or cross-over* or placebo*).tw.
40. ((treble or triple) adj blind*).tw.
41. or/29-40
42. Case Study/
43. case report*.tw.
44. (note or editorial).pt.
45. or/42-44
46. 41 not 45
47. 28 and 46
48. limit 47 to embase

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NOTES

Glossary

Allogeneic

The cells (blood cells or stem cells) come from someone other than the patient.

Cytopenia

The reduction of one or more blood cell types.

Dysplasia

Defects in stem cells can cause blood cells to have an abnormal shape or size.

Haematopoiesis

The production of red blood cells, white blood cells, and platelets from stem cells within the bone marrow.