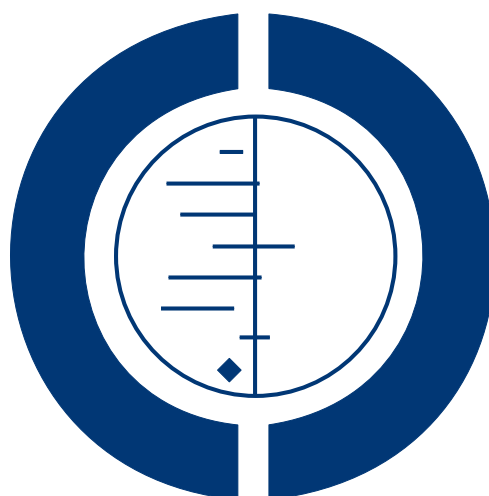


Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anaemia, and other congenital bone marrow failure disorders (Review)

Gu Y, Estcourt LJ, Doree C, Hopewell S, Vyas P



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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

Background

Bone marrow failure disorders include a heterogeneous group of disorders, of which myelodysplastic syndrome (MDS), forms the largest subgroup. MDS is predominantly a disease of the elderly, with many elderly people managed conservatively with regular allogeneic red blood cell (RBC) transfusions to treat their anaemia. However, RBC transfusions are not without risk. Despite regular transfusions playing a central role in treating such patients, the optimal RBC transfusion strategy (restrictive versus liberal) is currently unclear.

Objectives

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

Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2015, Issue 4), Ovid MEDLINE (from 1946), Ovid EMBASE (from 1974), EBSCO CINAHL (from 1937), the Transfusion Evidence Library (from 1980) and ongoing trial databases to 26th May 2015.

Selection criteria

RCTs including 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.

Data collection and analysis

We used standard Cochrane review methodology. One author initially screened all references, and excluded any that were clearly irrelevant or duplicates. Two authors then independently screened all abstracts of articles, identified by the review search strategy, for relevancy. Two authors independently assessed the full text of all potentially relevant articles for eligibility, completed the data extraction and assessed the studies for risk of bias using The Cochrane Collaboration's 'Risk of bias' tool.

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Main results

We included one trial (13 participants) and identified three ongoing trials that assess RBC transfusion strategies in people with MDS.

The quality of the evidence was very low across different outcomes according to GRADE methodology.

The one included study randomised participants to a restrictive [haemoglobin (Hb) transfusion trigger < 72 g/L, 8 participants] or liberal [Hb trigger < 96 g/L, 5 participants] transfusion policy. There was insufficient evidence to determine a difference in all-cause mortality (1 RCT; 13 participants; RR 0.13, 95% CI 0.01 to 2.32; very low quality evidence). There was insufficient evidence to determine a difference in the number of red blood cell transfusions (1 RCT; 13 participants; 1.8 units per patient per month in the liberal group, compared to 0.8 in the restrictive arm, no standard deviation was reported; very low quality evidence). There were no anaemia-related complications reported (cardiac failure) and no reported effect on activity levels (no statistics provided). The study did not report: mortality due to bleeding/infection/transfusion reactions or iron overload, quality of life, frequency and length of hospital admissions, serious infections (requiring admission to hospital), or serious bleeding (e.g. WHO/CTCAE grade 3 (or equivalent) or above).

Authors' conclusions

This review indicates that there is currently a lack of evidence for the recommendation of a particular transfusion strategy for bone marrow failure patients undergoing supportive treatment only. The one RCT included in this review was only published as an abstract and contained only 13 participants. Further randomised trials with robust methodology are required to develop the optimal transfusion strategy for such patients, particularly as the incidence of the main group of bone marrow failure disorders, MDS, rises with an ageing population.

PLAIN LANGUAGE SUMMARY

The optimum transfusion strategy for anaemic patients with bone marrow failure disorders receiving supportive treatment

Review Question

A restrictive transfusion policy involves giving a red blood cell transfusion if the oxygen-carrying capacity of blood (haemoglobin) falls below a certain level. A liberal transfusion policy involves giving a red blood cell transfusion at a higher haemoglobin level.

This review aims to assess whether a restrictive or liberal transfusion policy is superior in terms of death (due to any cause), death due to bleeding, infection, transfusion reactions or iron overload, quality of life, frequency and length of hospital admissions, serious bleeding or infections, and number of red blood cell transfusions required.

Background

The bone marrow is where many types of blood cells are produced. Red blood cells are necessary to bring oxygen to all parts of the body, white blood cells fight against infection, and platelets in the blood help to form clots and prevent bleeding. Bone marrow failure can have different causes and can happen at birth or later in life, and may result in too few of any or all of the three types of blood cells in the body. Too few red blood cells causes a low haemoglobin level, called anaemia, which may result in poor delivery of oxygen to the body. This can cause shortness of breath, tiredness and has a significant impact on quality of life.

Regular red blood cell transfusions are used to support patients and improve their quality of life when treatments that might cure the condition are not an option. However, there are certain risks involved with regular use of red blood cell transfusions, for example, transfusion reactions, transfusion-transmitted infections and iron overload.

Currently it is not clear if the best transfusion policy is a restrictive or liberal one.

Study Characteristics

Only one small study including 13 patients with bone marrow failure was included in this review. The study was funded by two government agencies and one charity. We are aware of three ongoing studies which have not yet been completed.

The evidence is current to 26th May 2015.

Key Results

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

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The one included study was too small to demonstrate any difference in all-cause mortality (death due to any cause) or number of red cell transfusions received between a restrictive compared to a liberal red blood cell transfusion policy. At the current time, there is a lack of evidence to recommend a restrictive transfusion strategy over a liberal one. Trials with good methodology are needed to determine the best transfusion policy for patients with long-term bone marrow failure disorders.

Quality of the Evidence

The evidence for the findings was of very low quality. This was because very small numbers of participants were included in the study. Only 13 patients were recruited to the trial rather than the planned 200 participants due to problems with recruitment.

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

Restrictive red blood cell transfusion compared with liberal red blood cell transfusion for patients with myelodysplastic syndrome						
Patient or population: patients with myelodysplastic syndrome Settings: 2 General and 1 University Hospital Intervention: Restrictive red blood cell transfusion policy (Hb trigger <72 g/L) Comparison: Liberal red blood cell transfusion policy (Hb trigger <96 g/L)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	[Liberal]	[Restrictive]				
All cause mortality	Low risk population		RR 0.13 (0.01 to 2.32)	13 (1 study)	⊕○○○ very low ^{1,2}	
	70 per 1000 ³	9 per 1000 (1 to 162)				
	Medium risk population					
	150 per 1000 ³	20 per 1000 (2 to 348)				
	High risk population					
	260 per 1000 ³	34 per 1000 (3 to 603)				
Mortality secondary to bleeding/ infection/transfusion re- actions or iron overload - not reported	not estimable	not estimable	not estimable	-	see comment	Not reported

Quality of life - not reported	not estimable	not estimable	not estimable	-	see comment	Not reported
Frequency and length of hospital admissions - not reported	not estimable	not estimable	not estimable	-	see comment	Not reported
Serious infections (requiring admission to hospital) - not reported	not estimable	not estimable	not estimable	-	see comment	Not reported
Serious bleeding (e.g. WHO/CTCAE grade 3 (or equivalent) or above) - not reported	not estimable	not estimable	not estimable	-	see comment	Not reported
Red blood cell transfusion requirements (units of red blood cells per patient per month)	not estimable	not estimable	not estimable	13 (1 study)	⊕○○○ very low ^{1,2}	The study reported a lower total transfused red cell amount in the restrictive versus liberal arm (0.8 units red cells per patient per month versus 1.8 units per patient per month) No statistical analysis of significance or further information was available from the study authors

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹Downgraded by 1 for imprecision, very small study with only 13 participants.

²Downgraded by 2 for risk of bias due to reporting bias, attrition bias, and other bias.

³The mortality data was based on data derived from a Kaplan Meier plot for the IPSS-R low, intermediate and high risk groups. Using information at one year from diagnosis ([de Swart 2015](#)).

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 blood 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 syndrome (MDS), acquired aplastic anaemia, and inherited 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 blood 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 guidelines in the UK or elsewhere for the recommendation of a particular transfusion strategy, restrictive (giving a red blood cell transfusion if the haemoglobin (Hb) falls below a certain low threshold) or liberal (giving a red blood 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 transplanta-

tion (HSCT), studied the effects of haemoglobin concentration on bleeding risk. It compared those transfused at a haemoglobin threshold of less than 80 g/L 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 blood 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 blood 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 people with aplastic anaemia treated later with an allogeneic bone marrow transplant (Kaminski 1990). Secondly, regular red blood cell transfusion, in the supportive treatment of low-risk MDS, results in raised serum ferritin, which together with transfusion dependence, act as independent adverse risk factors for survival in this group of people (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 very low in the UK (as a result of robust screening programmes), are still a significant problem in those countries with particularly high rates of HIV transmission. This is because there is a time-lag between a person becoming infected with HIV and the HIV test being positive (the window period can be three to six months if only an antibody test is used) (WHO 2009), the inability to test blood due to resource issues (WHO 2015), and ineffective screening of donors (WHO 2015).

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 people, data for which are limited. A prospective multicentre trial of 36 elderly low- and intermediate-risk MDS sufferers, 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 blood cell transfusion, showed an improvement in quality of life in terms of fatigue, dyspnoea, constipation and social functioning (Nilsson-Ehle 2011).

In the older population, particularly, where aggressive treatment may be inappropriate, a more supportive approach with regular red blood 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 blood 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 people 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 (Hébert 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 blood 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 blood cell transfusion strategy for such patients.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We included all people, irrespective of age, 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.

Types of interventions

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

Types of outcome measures

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) formulated the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

We searched for RCTs in the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2015, Issue 4) ([Appendix 1](#))
- Ovid MEDLINE (1946 to 26th May 2015) ([Appendix 2](#))
- Ovid EMBASE (1974 to 26th May 2015) ([Appendix 3](#))
- EBSCO CINAHL (1937 to 26th May 2015)
- PubMed (publications only)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to 26th May 2015)
- LILACS (1980 to 26th May 2015)
- IndMed (1986 to 26th May 2015)
- PakMediNet (1995 to 26th May 2015)
- KoreaMed (1958 to 26th May 2015)
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 26th May 2015)

We searched for ongoing RCTs to 26th May 2015 in the following databases.

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

We combined 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 combined searches in EMBASE and CINAHL with the relevant trial filters developed by the Scottish Intercollegiate Guidelines Network ([SIGN 2010](#)). We did not limit searches by year of publication, language or publication status.

Searching other resources

We also performed handsearches of the reference lists of included studies in order to identify further relevant studies. We made 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 selected studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) screened all search hits for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, two authors (YG, LE) independently screened all the remaining references for relevance against the full eligibility criteria. Full text articles were retrieved for all references for which a decision on eligibility could not be made from title and abstract alone. Study design features were assessed against the inclusion criteria. Additional information was requested from study authors as necessary to assess the eligibility for inclusion of individual studies. The two authors discussed the results of study selection and were able to resolve any discrepancies between themselves. The results of study selection was 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) independently extracted data onto standardised forms and performed a cross-check (Higgins 2011a). The data extraction form was piloted on two included RCTs. The review authors came to a consensus on the required changes. The review authors were not blinded to names of authors, institutions, journals or the study outcomes. The following information was 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 blood cell transfusion units received per patient; interval between red blood 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 assessed all RCTs for risk of bias 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) worked 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 review authors have assessed potential bias is reported in the 'Characteristics of included studies' table. A consensus on the degree of risk of bias was met through comparison of the review author's statements without the need for consultation with a third author. We did not use the 'Risk of bias' assessment to explore statistical heterogeneity in each included study and to perform sensitivity analyses because there was only one included study. We used the Cochrane tool for assessing risk of bias (low, high or unclear risk) in the following areas (Higgins 2011c).

- 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 recorded the mean, standard deviation, and total number of participants in both the treatment and control groups. For dichotomous outcomes we recorded the number of events and the total number of participants in both the treatment and control groups. If data allowed, we undertook quantitative assessments using Review Manager 5 (RevMan 2014).

We had planned to analyse continuous outcomes using the same scale, using the mean difference (MD) with 95% confidence intervals (CIs), and for continuous outcomes measured with different scales using the standard mean difference (SMD), however no meta-analyses were performed. We had planned to report hazard ratios (HRs) if available, for mortality data, however no HRs were reported, and we were unable to estimate the HR using the available data and a purpose built method based on the Parmar and Tierney tool (Parmar 1998; Tierney 2007).

We reported risk ratios (RRs) with a 95% CI (for mortality, as HRs were not available). We did not use the Peto Odds Ratio (OR) method for analysis (Deeks 2011) because the number of observed events was not small (< 5% of sample per group). We did not report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with CIs because there was insufficient evidence to determine a difference in any of the reported outcomes.

We provided a descriptive summary of the available data when the data could not be presented in any other format.

Unit of analysis issues

We did not encounter any specific unit of analysis issues associated with cluster-randomised trials, cross-over studies, and multiple observations for the same outcome. Should any studies of these designs have arisen, we had planned to treat these in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

Dealing with missing data

We contacted the authors of the four eligible studies to obtain further information, however no further data could be provided.

Assessment of heterogeneity

We did not perform an assessment of heterogeneity as it was not possible to perform meta-analysis due to only one study satisfying the eligibility criteria for inclusion.

Assessment of reporting biases

We were not able to perform an assessment of reporting bias due to lack of both outcome data and meta-analysis (Lau 2006; Sterne 2011).

Data synthesis

We performed 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 entered data into Review Manager 5 software (RevMan 2014). One review author (YG) entered the data and a second author (LE) then checked for accuracy. Meta-analysis was not possible because this review included only one study. We therefore provided a descriptive summary of the available information.

Summary of findings

We used 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 included (comparing a restrictive versus liberal transfusion strategy) are listed below.

1. All-cause mortality.
2. Mortality due 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 blood cell transfusion requirements.

Subgroup analysis and investigation of heterogeneity

We had planned to conduct the following subgroup analyses.

- Subgroup analysis for all bone marrow failure disorders.
 - Type of bone marrow failure disorders (myelodysplastic syndrome (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.

However, subgroup analysis was not possible due to the lack of outcome data.

Sensitivity analysis

We planned to 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.

Sensitivity analysis was not possible as no meta-analysis was performed.

R E S U L T S

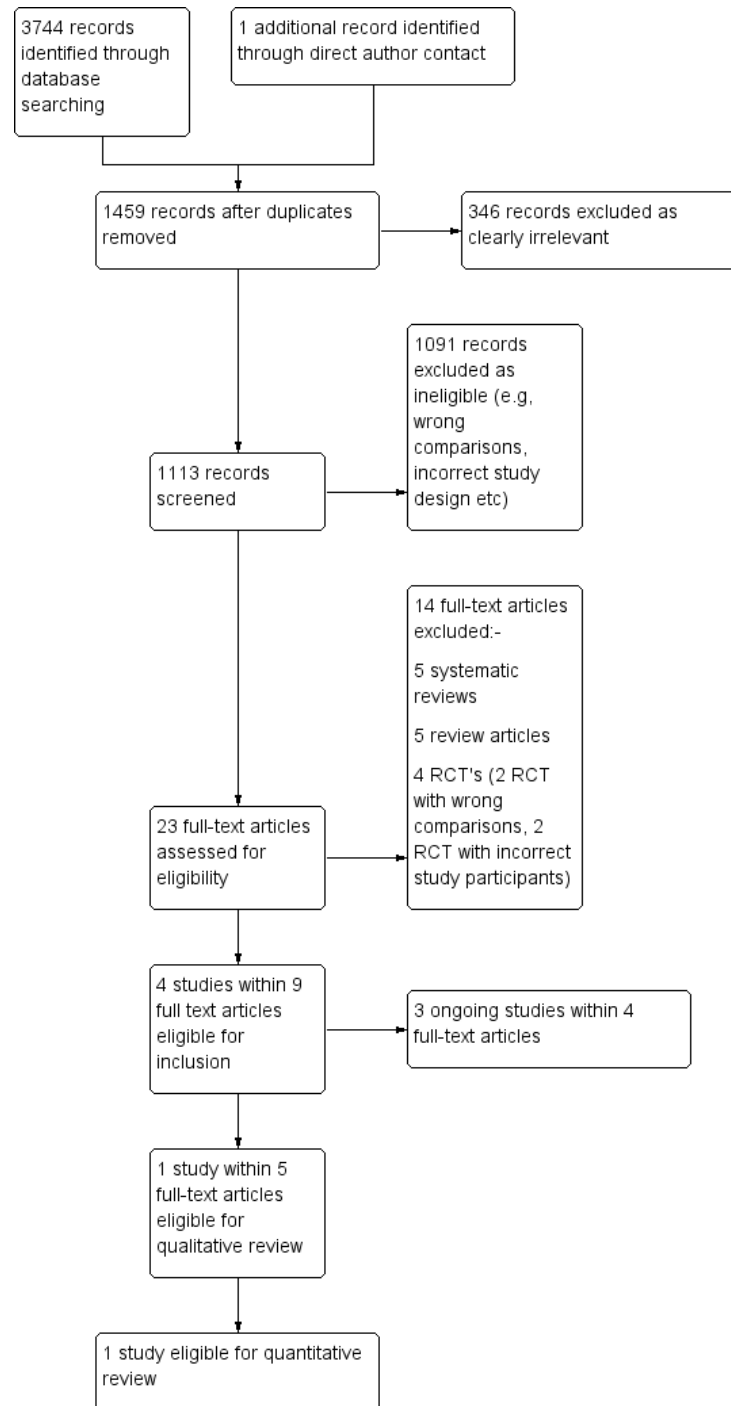
Description of studies

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

Results of the search

Please refer to the PRISMA flow diagram ([Figure 1](#)).

Figure 1. PRISMA Study flow diagram.



The main search was performed on 26th May 2015. A total of 3745 records were identified in the initial search, from which 2286 duplicates were removed, reducing the total records to 1459. From this, one author (CD) screened and removed 346 records that were clearly irrelevant (e.g. non-human). The remaining 1113 records were screened independently by two authors (YG, LE) against the inclusion criteria, from which 1091 records were excluded as ineligible, often due to incorrect study design or wrong comparisons. The remaining 21 records were obtained as full text articles, from which four studies were excluded as ineligible (two studies included transplant patients only, and two other studies analysed ineligible interventions). There remained a total of four studies eligible for inclusion (one completed and three ongoing studies).

Included studies

See [Characteristics of included studies](#) for full details of the study. Four studies met the inclusion criteria for the review but three of these studies are ongoing ([ISRCTN26088319](#); [NCT02099669](#); [NTR2684](#)) so are not eligible for inclusion in this review. One completed study ([Temple 2004](#)) was included within this review.

Study Design

The Temple study ([Temple 2004](#)) was a parallel-group multi-centre (two general and one university hospital), single-blinded RCT conducted in the Netherlands. This study has only been published as an abstract. The trial ran from July 2002 to June 2004.

Setting

The study was conducted in Holland with patients recruited from two general and one university hospital.

Participants

The study had originally planned to recruit 200 patients, however due to difficulties in recruitment, only 15 Myelodysplastic syndrome (MDS) patients were included in the study; four were classified as having refractory anaemia, five with refractory anaemia with ringed sideroblasts, four with refractory cytopenia with multilineage dysplasia, one with refractory anaemia with excess of blasts, and one with chronic myelomonocytic leukaemia. From this, 13 patients were randomised to either a restrictive or liberal transfusion policy.

Intervention and Comparator

This study compared a restrictive transfusion policy (haemoglobin transfusion trigger < 72 g/L) with a liberal transfusion trigger

(haemoglobin < 96 g/L) in terms of red blood cell usage and quality of life.

Co-interventions

There were no co-interventions in this study.

Outcomes

Quality of life was not reported, however there were no anaemia-related complications (e.g. cardiac failure and cerebrovascular ischaemia) or decrease in activity performance.

Funding Sources

The study was funded by two government agencies and one charity.

Ongoing Studies

There are three ongoing clinical trials ([NTR2684](#), [NCT02099669](#) and [ISRCTN26088319](#)). Please see [Characteristics of ongoing studies](#) for further details.

NTR2684

Trial [NTR2684](#) is a parallel-group open-label RCT that started on 1 January 2011, with a planned closing date of 31 December 2012. However, this study has not been completed and is not actively recruiting participants (e-mail correspondence with Dr Slomp). This trial is being conducted in the Netherlands. [NTR2684](#) plans to recruit 100 adults with myelodysplastic syndrome, chronic myelofibrosis and myeloproliferative conditions needing chronic transfusions as supportive care. It will compare transfusion with one unit of packed red blood cells versus two units of packed red blood cells if haemoglobin falls below 5.0mmol/L.

NCT02099669

Trial [NCT02099669](#) is a parallel-group open-label RCT planned to start in March 2014 with an estimated completion date of February 2016. The trial is running in Canada. [NCT02099669](#) plans to recruit 30 transfusion-dependent adults with myelodysplastic syndrome. It plans to compare a liberal transfusion strategy (maintaining Hb level between 110 g/L and 120 g/L) versus a restrictive transfusion strategy (maintaining Hb level between 85 g/L and 100 g/L).

ISRCTN26088319

Trial [ISRCTN26088319](#) is a parallel-group multicentre RCT conducted in the UK. The trial opened on 10th November 2014, and the recruitment end date is planned for 30th December 2016. [ISRCTN26088319](#) plans to recruit 38 transfusion-dependent adults with myelodysplastic syndrome (to include non-proliferative chronic myelomonocytic leukaemia (CMML) and other myeloproliferative/myelodysplastic (MPD/MDS) overlap syndromes). It will compare a restrictive transfusion strategy (maintain Hb level between 85 g/L and 100 g/L) versus liberal transfusion strategy (maintain Hb above 100 g/L).

Excluded studies

See [Characteristics of excluded studies](#) for full details of the studies. A total of 14 full-text articles were excluded. Of these:

- five were review articles ([Balducci 2006](#); [Bennett 1998](#); [Bowen 2010](#); [List 2006](#); [Neukirchen 2014](#))

- five were systematic reviews ([Brereton 2011](#); [Caocci 2009](#); [Clissa 2011](#); [Pinchon 2009](#); [Platzbecker 2012](#))

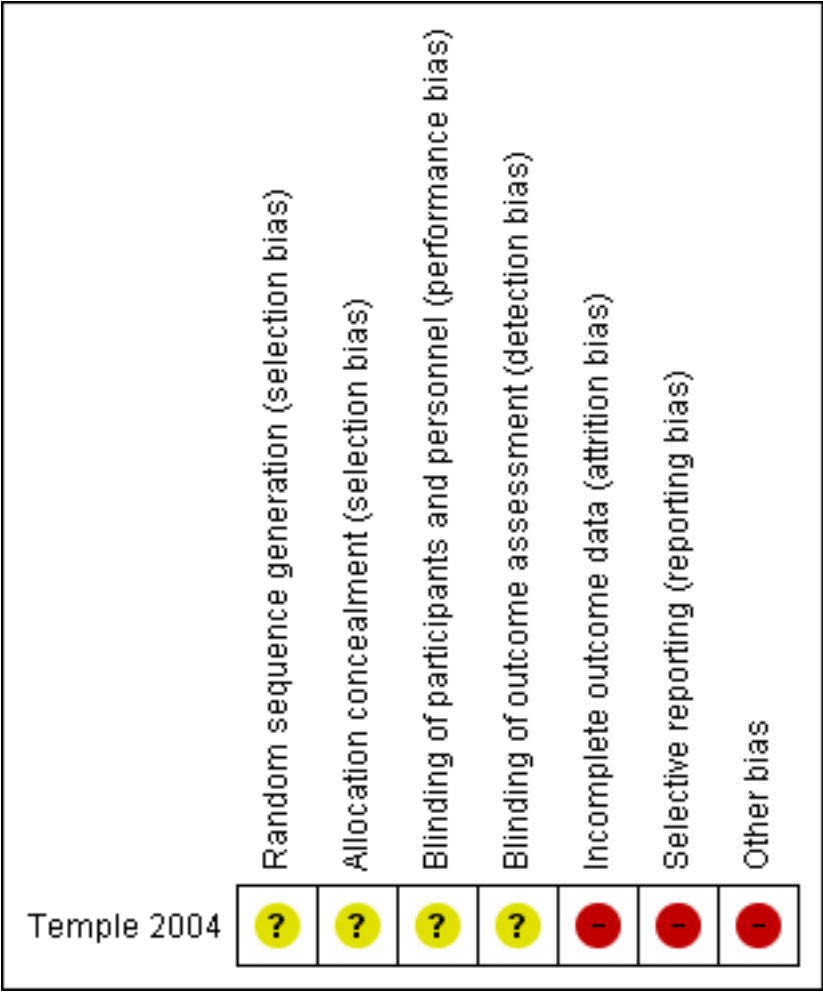
- four were RCT's comparing interventions or participants that did not meet our inclusion criteria:
 - two only recruited patients undergoing a haematopoietic stem cell transplant ([Robitaille 2013](#); [Tay 2011](#))
 - two compared different interventions that were not relevant to this review ([Chia 2010](#); [Efficace 2013](#)).

Risk of bias in included studies

Only one study was included in this review, and it was only published as an abstract, therefore it was not possible to assess risk of bias in the majority of cases due to a lack of information provided in the study abstract.

Please see [Figure 2](#) for a visual representation of the risk of bias in the included study. See the [Characteristics of included studies](#) section 'Risk of bias' table for further information about the bias identified within the trial.

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



Allocation

The risk of bias was unclear and could not be assessed due to a lack of information provided by the study abstract.

Blinding

There was an unclear risk of performance bias as the patients were blinded to their Hb value during the study period, but the method of blinding and confirmation that blinding had been achieved during the study was not reported. It was also not reported whether clinical staff were blinded to the intervention.

The risk of detection bias was unclear and could not be assessed due to lack of information provided by the study abstract.

Incomplete outcome data

Losses to follow up were reported in the study abstract. Following randomisation, a total of two patients died in the liberal group, and one patient withdrew consent in the restrictive arm. However, it is not clear if and how these patient data were included in the final analysis of mean Hb, amount of transfused red cells and anaemia related complications. The mean follow up period in the liberal group was 6.2 months (inclusive run in period) and 7.4 months for the restrictive group. Patients were planned to be followed up for 12 months (excluding run in period of three months).The risk of bias was therefore high.

Selective reporting

There was evidence of a high risk of reporting bias in this study abstract as a number of primary and secondary outcomes were not reported, despite intention to collect, as described in the trial registration. The following planned outcomes were not reported. Primary outcome measure.

1. Fatigue.

Secondary outcome measures.

1. Health Related Quality of Life (HRQoL).
2. Blood usage and the costs.
3. Haemoglobin increase after transfusion.
4. Heart beat, blood pressure, temperature, platelet count.
5. Development of RBC alloantibodies.

Other potential sources of bias

The planned study recruitment for the [Temple 2004](#) was 200 patients, however the study was stopped early due to poor recruitment. The numbers of participants in each study arm was very small, with only eight patients in the restrictive arm and five patients in the liberal arm.

Effects of interventions

See: [Summary of findings for the main comparison](#)

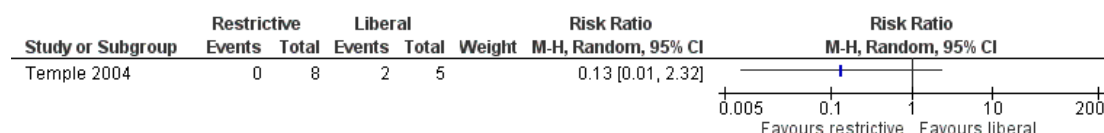
Primary outcomes

We were not able to categorise all outcomes according to short-, medium-, and long-term outcomes due to the limited data available. We were also not able to report the exact definition of these time frames over time periods that were common to as many studies as possible (for example, up to 30 days, one to six months, and greater than six months), again due to limited data.

All-cause mortality

In the [Temple 2004](#) study, during the run-in period of three months when all 15 patients included in the study were transfused with Hb trigger < 96 g/L, there were two patient deaths prior to randomisation. The cause of death was not reported. Post randomisation, two patients out of five allocated to the liberal transfusion policy died. No patient deaths were reported in the restrictive arm. Again, the cause of death was not reported. There was insufficient evidence to determine a difference in all-cause mortality between a restrictive [haemoglobin (Hb) transfusion trigger < 72 g/L, eight participants] or a liberal [Hb trigger < 96 g/L, five participants] transfusion policy (RR 0.13, 95% CI 0.01 to 2.32; very low quality evidence). ([Figure 3](#)).

Figure 3. Forest plot of comparison: I Liberal versus restrictive, outcome: I.I All cause mortality.



Mortality due to bleeding, infection, transfusion reactions, or iron overload

We were unable to report on mortality due to bleeding, infection, transfusion reactions, or iron overload, or both, due to lack of available data. No studies reported this outcome.

Secondary outcomes

The only secondary outcome we were able to report on was red blood cell transfusion requirements in terms of number of units required, but not number of transfusion episodes or intervals due to lack of available data. We were not able to report on any of the other secondary outcomes.

Frequency and length of hospital admissions

No studies reported this outcome.

Frequency and length of intensive care admission

No studies reported this outcome.

Quality of life (measured using validated scales, for example, EQ-5D, FACT-AN, and EORTC-30)

No studies reported this outcome.

In the [Temple 2004](#) study fatigue measured using the Multidimensional Fatigue Index 20 (MFI20) was reported as the primary outcome measure in the clinical trial register for this study. The Short Form 36 (SF-36) and EuroQol 5D were reported as sec-

ondary outcomes. However, no results were given for these outcomes in the published abstract report.

Non-fatal serious adverse events classified as:

Serious bleeding (e.g. WHO / CTCAE grade 3 or above or equivalent)

No studies reported this outcome.

Adverse transfusion reactions (including, but not limited to transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), ABO mismatched transfusions and transfusion transmitted infection (TTI))

No studies reported this outcome.

Iron overload (defined by ferritin > 1000 or clinical symptoms, or signs of iron overload, or all three)

No studies reported this outcome.

Serious infections (infections requiring admission to hospital)

No studies reported this outcome.

Blood product requirement

Red blood cell transfusion requirements (for example, number of units required or number of transfusion episodes) and intervals

In the [Temple 2004](#) study there was insufficient evidence to determine a difference in the amount of red blood cell transfusions (1.8 units per patient per month in the liberal group, compared to 0.8 in the restrictive arm, no standard deviation was reported; very low quality evidence).

Platelet transfusion requirements (for example, number of pools required, or number of transfusion episodes) and intervals

No studies reported this outcome.

Usage of iron chelation therapy

No studies reported this outcome.

DISCUSSION

Summary of main results

A total of four RCTs met the inclusion criteria, however three studies ([ISRCTN26088319](#), [NCT02099669](#), [NTR2684](#)) are ongoing, with only one study ([Temple 2004](#)) being completed. This study randomised a total of 13 patients with MDS to a liberal or restrictive transfusion strategy. There was insufficient evidence to determine a difference in all-cause mortality (RR 0.13, 95% CI 0.01 to 2.32). There was insufficient evidence to determine a difference in the number of red blood cell transfusions. No anaemia-related complications were reported. No studies reported on mortality secondary to bleeding, infection, transfusion reactions or iron overload; quality of life; frequency and length of hospital admissions; serious infections (requiring admission to hospital); or serious bleeding (e.g. WHO/CTCAE grade 3 (or equivalent) or above).

Overall completeness and applicability of evidence

Conclusions drawn using the data extracted from this systematic review are very limited by the inclusion of only one RCT ([Temple 2004](#)) with a small number of participants. The [Temple 2004](#) study reported on only one of this review's primary outcomes, all-cause mortality, and on one secondary outcome, red blood cell transfusion requirements. Due to the small numbers of participants in this study, there is insufficient evidence at present to draw any firm conclusions. The [Temple 2004](#) study did not report on several of this review's outcomes, including mortality due to bleeding, infection, transfusion reactions, or iron overload, or both; frequency and length of hospital admissions; frequency and length of intensive care admission; serious bleeding; adverse transfusion reactions; iron overload; serious infections; platelet transfusion requirements; and usage of iron chelation therapy. This highlights the ongoing lack of data for these outcomes. Nevertheless, we identified three ongoing studies ([ISRCTN26088319](#), [NCT02099669](#), [NTR2684](#)) randomising participants to either a liberal or restrictive transfusion strategy with aims to measure many of the above outcomes. When complete, the results of all four RCTs taken together should provide more meaningful conclusions. These ongoing studies plan to complete recruitment by December 2016.

Quality of the evidence

The [Temple 2004](#) study was published only in abstract form, and assessment of selection bias was not possible due to lack of information. With regards to blinding, the risk of bias here is unclear, as although the participants were blinded to their haemoglobin result, the method and assessment of blinding was not reported.

Blinding of clinical staff to the intervention was also not reported. There was high attrition bias as it was not clear if and how the patients were lost to follow up (two deaths in the liberal group and one patient withdrew consent in the restrictive arm) however follow-up was much shorter than planned (mean 6.2 to 7.4 months versus planned 15 months). Reporting bias risk was high due to a number of both primary and secondary outcomes not reported, despite intention to collect, as detailed in the trial registration. Finally, other risks of bias include the trial stopping earlier than planned due to poor recruitment, and a discrepancy noted between two published versions of the study abstract with regards to the dates reported for the recruitment timeline. It is not clear which is the correct recruitment time period. Overall, taking the above into account, high risk of bias exists for this study, and the quality of evidence is therefore very low.

Overall the quality of the evidence was rated as very low across different outcomes according to GRADE methodology (Schünemann 2011b) (Summary of findings for the main comparison). This was due to the study being at high risk of bias, and the outcome estimates being imprecise.

Two outcomes were considered very low grade quality evidence according to GRADE methodology due to the very serious risk of bias of the included studies (see above) and the serious imprecision of the estimates.

- All-cause mortality.
- Red blood cell transfusion requirements.

The reason for the imprecision is because of the small number of participants within the trial and the low number of events. None of the other outcomes of this review were reported.

Potential biases in the review process

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

We pre-specified all outcomes and subgroups prior to analysis.

Only one study was included in this review so no meta-analyses could be performed, and publication bias by the use of a funnel plot could not be performed.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other systematic reviews that report on this topic. None of the systematic reviews excluded within this review (Brereton 2011; Caocci 2009; Clissa 2011; Pinchon 2009; Platzbecker 2012) included studies that compared a restrictive versus liberal red cell transfusion strategy.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review indicate that there is currently very limited evidence available to recommend a particular transfusion strategy for patients with bone marrow failure requiring supportive treatment. The only data available are extracted from one RCT. This trial recruited very small numbers of patients (13 participants) and it is currently not possible to recommend one transfusion strategy over another for the supportive management of patients with bone marrow failure.

Implications for research

As the incidence of MDS rises with an ageing population, many of whom are unable to tolerate curative therapy, further clinical trials with robust methodology are now required to develop the optimal transfusion strategy for such people.

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Gu Y, Estcourt LJ, Doree C, Trivella M, Hopewell S, Vyas P. Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anaemia, and other congenital bone marrow failure disorders. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD011577]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Temple 2004

Methods	Type of study: parallel-group, multi-centre, single-blinded randomised controlled trial Type of publication: abstract. Country: The Netherlands. Number of centres: three (two general and one university hospital) Dates of trial (July 2002 to June 2004). Treatment Period and follow-up: three months run-in period, mean follow-up period of 6.2 -7.4 months
Participants	15 adult patients with MDS were included in the study, and 13 were randomised to 1. restrictive [haemoglobin (Hb) transfusion trigger < 72 g/L, eight patients]; 2. liberal [Hb trigger < 96 g/L, five patients] transfusion policy
Interventions	Restrictive [haemoglobin (Hb) transfusion trigger < 72 g/L] versus liberal [Hb trigger < 96 g/L] transfusion policy
Outcomes	Primary outcome measure: Fatigue. Secondday outcome measures. 1. Health Related Quality of Life (HRQoL). 2. Blood usage and the costs. 3. Haemoglobin increase after transfusion. 4. Heart beat, blood pressure, temperature, platelet count. 5. Development of RBC alloantibodies. 6. Mortality.
Notes	Sources of funding. 1. The Netherlands Ministry of Health, Welfare and Sport (The Netherlands). 2. National Institute of Public Health and Environmental Protection (RIVM) (The Netherlands) 3. Friends of the Blood Transfusion Foundation (Stichting Vriendenvan de Bloedtransfusie) (The Netherlands)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This information was not provided in the abstract.
Allocation concealment (selection bias)	Unclear risk	This information was not provided in the abstract.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded to the Hb results during the study period, however the method of blinding and assessment of testing whether blinding maintained was not reported. It was not reported whether clinical staff were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This information was not provided in the abstract.
Incomplete outcome data (attrition bias) All outcomes	High risk	Eight patients were randomised for the restrictive transfusion policy and five patients for the liberal transfusion policy. Two patients in the restrictive arm completed the study. The mean follow up period in the liberal group was 6.2 months (inclusive run in period) and 7.4 months for the restrictive group. Patients were planned to be followed up for 12 months (excluding run in period of three months)
Selective reporting (reporting bias)	High risk	The outcomes that were reported in the trial registration document were: Primary outcome measure(s). 1.Fatigue - not reported in abstract. Secondary outcome measure(s). 1. Health Related Quality of Life (HRQoL) - not reported in abstract. 2. Blood usage and the costs - costs not reported in abstract. 3. Haemoglobin increase after transfusion - not reported in abstract. 4. Heart beat, blood pressure, temperature, platelet count - not reported in abstract. 5. Development of RBC alloantibodies - not reported in abstract. 6. Mortality - reported in abstract.
Other bias	High risk	Only eight patients were randomised in the restrictive arm and five patients in the liberal arm. The planned recruitment was 200 patients, the study was stopped early due to poor recruitment. The Temple 2004 study was published as an abstract only, and no detailed full-text article was ever published, this was confirmed after contacting the lead

	author
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Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Balducci 2006	This is a review article.
Bennett 1998	This is a review article.
Bowen 2010	This is a review article.
Brereton 2011	Study design: systematic review.
Caocci 2009	Study design: systematic review.
Chia 2010	Intervention: compared QOL between transfusion of fresh versus standard issue blood in highly transfusion-dependent patients
Clissa 2011	Study design: systematic review.
Efficace 2013	Intervention: investigation of impact of deferasirox on quality of life of lower-risk transfusion dependent MDS
List 2006	This is a review article.
Neukirchen 2014	This is a review article.
Pinchon 2009	Study design: systematic review.
Platzbecker 2012	Study design: systematic review.
Robitaille 2013	Participants: patients undergoing allogeneic bone marrow transplant
Tay 2011	Participants: patients undergoing haematopoietic stem cell transplant

Characteristics of ongoing studies [ordered by study ID]

ISRCTN26088319

Trial name or title	Red blood cell transfusion and QOL in myelodysplastic syndrome
Methods	Parallel-group multicentre randomised controlled trial (a feasibility study)

Participants	38 transfusion-dependent adult patients with myelodysplastic syndrome including non-proliferative CMML and other MDS/MPD overlap syndromes
Interventions	Restrictive transfusion strategy (maintain Hb level between 85 g/L and 100 g/L) versus liberal transfusion strategy (maintain Hb above 100 g/L)
Outcomes	<p>Primary outcome measures: percentage compliance of pre-transfusion haemoglobin concentrations being within or above the target range, achievement of at least a 20 g/L difference between the mean pre-transfusion haemoglobins in the two arms</p> <p>Secondary outcome measures: number of patients ineligible due to screening failure or workload of department; enrolment rates; percentage compliance with completing the QoL questionnaires; ability of patients to remain blinded to the treatment arm; proportion of transfusions and proportion of patients with all transfusions given correctly; percentage of pre-transfusion haemoglobin concentrations falling below, within and above the target range of the red blood cell transfusion thresholds; magnitude of change in physical functioning, fatigue, dyspnoea and global health scores on the EORTC QLQ-C30; numbers of adverse events and transfusion reactions; the overall utilisation of blood</p>
Starting date	10/11/2014
Contact information	Ms Claire Foley (claire.foley@nhsbt.nhs.uk)
Notes	Recruitment end date: 30/12/2016 Sponsor: NHSBT

NCT02099669

Trial name or title	Red Blood Cell Transfusion Thresholds and QOL in MDS (EnhanceRBC)
Methods	Parallel-group, open-label randomised controlled trial.
Participants	30 transfusion-dependent adult patients with myelodysplastic syndrome
Interventions	Liberal transfusion strategy (maintaining Hb level between 110 g/L and 120 g/L) versus restrictive transfusion strategy (maintaining Hb level between 85 g/L and 100g/L)
Outcomes	<p>Primary Outcome Measures: percentage compliance of twice weekly haemoglobins</p> <p>Secondary outcome measures: measures of feasibility (number of patients ineligible due to screen failure, enrolment rates defined by the number of enrolled patients/month, percentage compliance with QOL questionnaire completion at least 3 serial times, other logistical issues related to protocol implementation, recruitment rates, randomisation implementation strategy, data collection, patient tolerability of study schedule), Quality of life (the magnitude of change in physical functioning, fatigue, dyspnoea and global health scores on the EORTC QLQ-C30, calculated health utility on the EQ-5D and fatigue score on FACT-F), adverse events (the rate of transfusion reactions, rate of adverse events such as cardiac events and thromboembolic events), alloimmunization rates, haemosiderosis (the impact on transfusion associated haemosiderosis rates and burdens, overall utilization of blood, time commitment) the overall time commitment per group, measured as the time spent in transfusion medicine clinic</p>

NCT02099669 (Continued)

Starting date	March 2014
Contact information	Kristina Commisso (Kristina.Commisso@ sunnybrook.ca)
Notes	Estimated completion date: February 2016

NTR2684

Trial name or title	Transfusion as supportive care for the improvement of quality of life
Methods	Parallel-group, open-label randomised controlled trial.
Participants	100 adult patients with myelodysplastic syndrome, chronic myelofibrosis and myeloproliferative conditions needing chronic transfusions as supportive care
Interventions	Transfusion with one unit packed red cells versus two units of packed red cells if Hb concentration falls below 5.0 mmol/l
Outcomes	Primary outcome measure: quality of life assessed with the EORTC QLQ C-30 questionnaire Secondary outcome measures: number of transfusion units, transfusion frequency, average Hb concentration before transfusion, number and duration of hospital visits
Starting date	1st January 2011
Contact information	Contact for public queries: A.W. Duyts Contact for scientific queries: Dr. J. Slomp
Notes	Planned closing date was 31st December 2012. This study is not actively recruiting patients (e-mail correspondence with Dr Slomp)

DATA AND ANALYSES

Comparison 1. Liberal versus restrictive

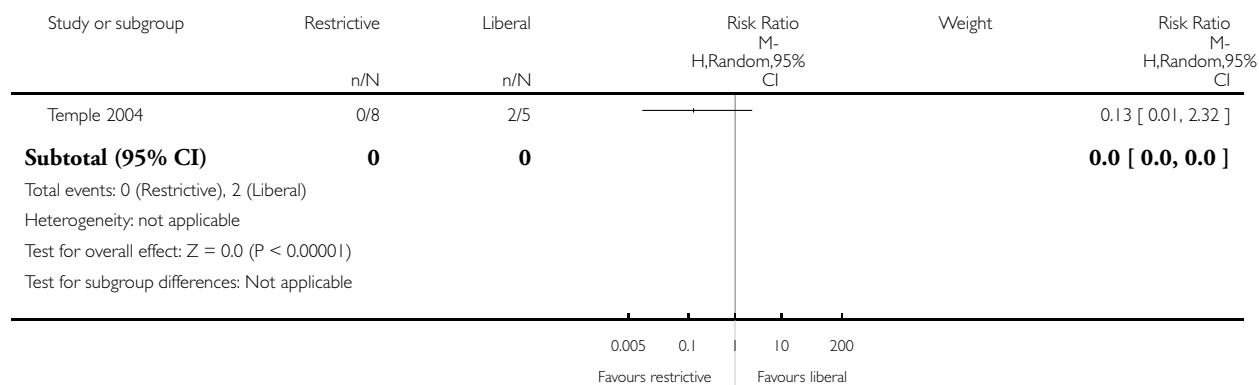
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Liberal versus restrictive, Outcome 1 All cause mortality.

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

Comparison: 1 Liberal versus restrictive

Outcome: 1 All cause mortality



APPENDICES

Appendix 1. 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. (smo?ldering* 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. (smoldering* 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

CONTRIBUTIONS OF AUTHORS

Yisu Gu: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis; content expert; and review development.

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

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

Sally Hopewell: protocol development; methodological expert; and review development.

Paresh Vyas: protocol development; content expert; and review development.

DECLARATIONS OF INTEREST

Yisu Gu: none known.

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several differences between the protocol ([Gu 2015](#)) and this review due to lack of data.

We were not able to categorise all outcomes according to short-, medium-, and long-term outcomes due to lack of outcome data available.

We were not able to report on the primary outcome of mortality due to bleeding, infection, transfusion reactions, or iron overload, or both, due to lack of outcome data available.

We were not able to report on the following secondary outcomes due to lack of data available.

- Frequency and length of hospital admissions.
- Frequency and length of intensive care admissions.
- Non-fatal serious adverse events classified as:
 - serious bleeding;
 - adverse transfusion reactions;
 - iron overload;
 - serious infections.
- Blood product requirement:
 - Platelet transfusion requirements (for example, number of pools required, or number of transfusion episodes) and intervals.
- Usage of iron chelation therapy.

As only one RCT ([Temple 2004](#)) was eligible for inclusion, it was not possible to perform any meta-analysis.

We were not able to assess any publication bias due to the inclusion of only one RCT.

We were not able to perform any subgroup analysis, comparing different types of bone marrow failure disorders, acquired aplastic anaemia versus inherited childhood bone marrow failure disorders, high versus low-risk MDS, or paediatric versus adult versus elderly patients.

We were not able to perform sensitivity analysis due to lack of available data.

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.

Erythropoietin

A substance given to anaemic patients to increase production of red blood cells.

Ferritin

A marker used to measure the amount of iron in the body. High levels may signify iron overload.

Haematopoiesis

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

Neutropenia

Lower than normal numbers of neutrophils (a type of white blood cell needed to fight infections).

Thrombocytopenia

Lower than normal numbers of platelets.