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Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support (Review)

Estcourt LJ, Malouf R, Trivella M, Fergusson DA, Hopewell S, Murphy MF

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[Intervention Review]

Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

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ABSTRACT

Background

Many people diagnosed with haematological malignancies experience anaemia, and red blood cell (RBC) transfusion plays an essential supportive role in their management. Different strategies have been developed for RBC transfusions. A restrictive transfusion strategy seeks to maintain a lower haemoglobin level (usually between 70 g/L to 90 g/L) with a trigger for transfusion when the haemoglobin drops below 70 g/L), whereas a liberal transfusion strategy aims to maintain a higher haemoglobin (usually between 100 g/L to 120 g/L, with a threshold for transfusion when haemoglobin drops below 100 g/L). In people undergoing surgery or who have been admitted to intensive care a restrictive transfusion strategy has been shown to be safe and in some cases safer than a liberal transfusion strategy. However, it is not known whether it is safe in people with haematological malignancies.

Objectives

To determine the efficacy and safety of restrictive versus liberal RBC transfusion strategies for people diagnosed with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without a haematopoietic stem cell transplant (HSCT).

Search methods

We searched for randomised controlled trials (RCTs) and non-randomised trials (NRS) in MEDLINE (from 1946), Embase (from 1974), CINAHL (from 1982), Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 6), and 10 other databases (including four trial registries) to 15 June 2016. We also searched grey literature and contacted experts in transfusion for additional trials. There was no restriction on language, date or publication status.

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Selection criteria

We included RCTs and prospective NRS that evaluated a restrictive compared with a liberal RBC transfusion strategy in children or adults with malignant haematological disorders or undergoing HSCT.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

We identified six studies eligible for inclusion in this review; five RCTs and one NRS. Three completed RCTs (156 participants), one completed NRS (84 participants), and two ongoing RCTs. We identified one additional RCT awaiting classification. The completed studies were conducted between 1997 and 2015 and had a mean follow-up from 31 days to 2 years. One study included children receiving a HSCT (six participants), the other three studies only included adults: 218 participants with acute leukaemia receiving chemotherapy, and 16 with a haematological malignancy receiving a HSCT. The restrictive strategies varied from 70 g/L to 90 g/L. The liberal strategies also varied from 80 g/L to 120 g/L.

Based on the GRADE rating methodology the overall quality of the included studies was very low to low across different outcomes. None of the included studies were free from bias for all 'Risk of bias' domains. One of the three RCTs was discontinued early for safety concerns after recruiting only six children, all three participants in the liberal group developed veno-occlusive disease (VOD).

Evidence from RCTs

A restrictive RBC transfusion policy may make little or no difference to: the number of participants who died within 100 days (two trials, 95 participants (RR: 0.25, 95% CI 0.02 to 2.69, *low-quality evidence*); the number of participants who experienced any bleeding (two studies, 149 participants; RR:0.93, 95% CI 0.73 to 1.18, low-quality evidence), or clinically significant bleeding (two studies, 149 participants, RR: 1.03, 95% CI 0.75 to 1.43, *low-quality evidence*); the number of participants who required RBC transfusions (three trials; 155 participants: RR: 0.97, 95% CI 0.90 to 1.05, *low-quality evidence*); or the length of hospital stay (restrictive median 35.5 days (interquartile range (IQR): 31.2 to 43.8); liberal 36 days (IQR: 29.2 to 44), *low-quality evidence*).

We are uncertain whether the restrictive RBC transfusion strategy: decreases quality of life (one trial, 89 participants, fatigue score: restrictive median 4.8 (IQR 4 to 5.2); liberal median 4.5 (IQR 3.6 to 5) (*very low-quality evidence*); or reduces the risk of developing any serious infection (one study, 89 participants, RR: 1.23, 95% CI 0.74 to 2.04, *very low-quality evidence*).

A restrictive RBC transfusion policy may reduce the number of RBC transfusions per participant (two trials; 95 participants; mean difference (MD) -3.58, 95% CI -5.66 to -1.49, *low-quality evidence*).

Evidence from NRS

We are uncertain whether the restrictive RBC transfusion strategy: reduces the risk of death within 100 days (one study, 84 participants, restrictive 1 death; liberal 1 death; *very low-quality evidence*); decreases the risk of clinically significant bleeding (one study, 84 participants, restrictive 3; liberal 8; *very low-quality evidence*); or decreases the number of RBC transfusions (adjusted for age, sex and acute myeloid leukaemia type geometric mean 1.25; 95% CI 1.07 to 1.47 - data analysis performed by the study authors)

No NRS were found that looked at: quality of life; number of participants with any bleeding; serious infection; or length of hospital stay.

No studies were found that looked at: adverse transfusion reactions; arterial or venous thromboembolic events; length of intensive care admission; or readmission to hospital.

Authors' conclusions

Findings from this review were based on four studies and 240 participants.

There is low-quality evidence that a restrictive RBC transfusion policy reduces the number of RBC transfusions per participant. There is low-quality evidence that a restrictive RBC transfusion policy has little or no effect on: mortality at 30 to 100 days, bleeding, or hospital stay. This evidence is mainly based on adults with acute leukaemia who are having chemotherapy. Although, the two ongoing studies (530 participants) are due to be completed by January 2018 and will provide additional information for adults with haematological malignancies, we will not be able to answer this review's primary outcome. If we assume a mortality rate of 3% within 100 days we would need 1492 participants to have a 80% chance of detecting, as significant at the 5% level, an increase in all-cause mortality from 3% to 6%. Further RCTs are required in children.

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PLAIN LANGUAGE SUMMARY

Restrictive or liberal red blood cell transfusion policies for people with blood cancer

Review question

To determine the benefit and harm of a restrictive red blood cell transfusion strategy when compared with a liberal red blood cell transfusion strategy for people diagnosed with a blood cancer (for example leukaemia, lymphoma, myeloma) who were receiving intensive treatments for their disease (chemotherapy or stem cell transplantation).

Background

People with blood cancers often have anaemia (low haemoglobin level) due to their underlying cancer or its treatment (chemotherapy or a stem cell transplant. Haemoglobin is essential for carrying oxygen around the body.

A red blood cell transfusion is given to increase the haemoglobin level to prevent symptoms of anaemia occurring, or to treat symptoms of anaemia. The decision to give a red cell transfusion should balance its benefits with its potential risks (e.g. rash, fever, chills, developing breathing problems). These reactions are usually mild and easily treated, severe reactions to red blood cell transfusions are extremely rare. In high-income countries the likelihood of getting an infection from a red blood cell transfusion is very low, however the risk is much higher in low-income countries. The need for a red cell transfusion is usually guided by the haemoglobin level. In people with other conditions a transfusion is usually given if the haemoglobin level drops to around 70 g/L to 80 g/L (restrictive transfusion strategy). People with blood cancers may benefit from a higher haemoglobin level (100 g/L to 120g/L, liberal transfusion strategy), they may bleed less and have an improved quality of life. In people undergoing surgery or people who are admitted to intensive care units a restrictive transfusion strategy has been shown to be as safe as, or safer than a liberal transfusion strategy.

Study characteristics

We searched for randomised and prospective non-randomised trials. Six studies met our inclusion criteria, four are completed and two are still ongoing. An additional study is awaiting classification. The completed studies were conducted between 1997 and 2015 and included 240 participants. One study included children receiving a stem cell transplant and it was stopped early due to safety concerns (six children), the other three studies only included adults, 218 adults with acute leukaemia receiving chemotherapy, and 16 with a blood cancer receiving a stem cell transplant. Three studies were randomised controlled trials and the fourth was a non-randomised study. The haemoglobin threshold of the restrictive strategies varied across the studies.

The sources of funding were reported in all four studies. One study was industry sponsored.

Key results

The evidence is current to June 2016 and is mainly based on adults with acute leukaemia who are having chemotherapy.

A restrictive red blood cell transfusion policy may reduce the number of red blood cell transfusions received by an individual.

A restrictive red blood cell transfusion policy may have little or no effect on: whether an individual receives a red blood cell transfusion; death due to any cause; bleeding; or hospital stay.

We are uncertain whether a restrictive red blood cell transfusion policy affects quality of life, or the risk of developing a serious infection.

No studies were found that looked at: adverse reactions to transfusion; development of blood clots; length of stay in intensive care; or need to be readmitted to hospital.

There are two ongoing trials (planning to recruit 530 adults) that are due to be completed by January 2018 and will provide additional information for adults with blood cancers. There are no ongoing trials in children.

Quality of evidence

The overall quality of the evidence was very low to low as the included studies were at considerable risk of bias, the estimates were imprecise, and most of the evidence was only for adults with acute leukaemia.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Restrictive compared with liberal for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Patient or population: people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support
Setting: Hospitals, haematology centres
Intervention: Restrictive
Comparison: Liberal red blood cell transfusion RCTs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with liberal red blood cell transfusion RCTs	Risk with Restrictive				
All-cause mortality at 31 to 100 days	Study population 61 per 1000	**15 per 1000** (1 to 163)	**RR 0.25** (0.02 to 2.69)	95 (2 RCTs)	⊕⊕◯◯ LOW[1]	
Quality of life	**Liberal group:** median 4.5 (IQR: 3.6 to 5) **Restrictive:** median 4.8 (IQR: 4 to 5.2)[a]			89 (1 RCT)	⊕⊕◯◯ VERY LOW[2,3,4]	
Number of participants with any bleeding	Study population 639 per 1,000	**595 per 1000** (467 to 754)	**RR 0.93** (0.73 to 1.18)	149 (2 RCTs)	⊕⊕◯◯ LOW[2,3]	
Number of participants with clinically significant bleeding	Study population 443 per 1,000	**456 per 1000** (332 to 633)	**RR 1.03** (0.75 to 1.43)	149 (2 RCTs)	⊕⊕◯◯ LOW[2,3]	
Serious infections	Study population 400 per 1,000	**492 per 1000** (296 to 816)	**RR 1.23** (0.74 to 2.04)	89 (1 RCT)	⊕◯◯◯ VERY LOW[2,3,4]	
Length of hospital admission (days)	**Liberal:** median 36 days (IQR: 29.2 to 44) **Restrictive**: median: 35.5 days (IQR: 31.2 to 43.8)			89 (1 RCT)	⊕⊕◯◯ LOW[2,3]	

Hospital readmission rate - not reported	-	-	-	-	-

*__The risk in the intervention group__ (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]The level of evidence was downgraded by 2 due to imprecision.
[2]The level of evidence was downgraded by 1 due to imprecision.
[3] The level of evidence was downgraded by 1 due to indirectness, the studies only included adults.
[4]The level of evidence was downgraded by 1 due to risk of bias (unblinded study).
[a]This is a ten-point scale with a score of zero indicating no fatigue and a score of ten indicating the worst possible fatigue.
The median fatigue scare was similar for both groups; P = 0.53.
Interquartile range: IQR

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BACKGROUND

Description of the condition

Approximately 30% to 100% of people diagnosed with haematological malignancies experience anaemia during the course of their disease and red blood cell (RBC) transfusions play an essential supportive role in their management (Knight 2004). Intensive chemotherapy administered to treat people with haematological malignancies often results in prolonged periods of myelosuppression necessitating frequent RBC transfusions, especially in the setting of haematopoietic stem cell transplantation (HSCT). Indeed, people with haematology-oncology medical conditions are amongst the largest consumers of RBC transfusions (Borkent-Raven 2010; Javadzadeh Shahshahani 2015; Tinegate 2016; Whitaker 2015).
Of an estimated 108 million blood donations collected worldwide, over 50% are collected in high-income countries, which represent only 18% of the world's population (WHO 2015). Blood availability, distribution and safety vary widely throughout the world. In developing countries, blood supply is inadequate and the most common source is family or paid blood donors (WHO 2015). The prevalence of transfusion-transmissible infections (TTI) in blood donations is extremely low in high-income countries but is significantly higher in low- and middle-income countries (Table 1; Bolton-Maggs 2014). Although all donated blood should be screened for infections before use, currently 25 countries are not able to screen for one or more of the minimum mandatary blood screening infections: human immunodeficency virus (HIV), hepatitis B (HBV), hepatitis C (HCV) and syphilis (Table 2; WHO 2015). Irregular supply of test kits is one of the most commonly reported barriers to screening blood donations (WHO 2015). As well as the risk from infection, the risk of immune modulation, alloimmunisation, and iron overload are not uncommon events associated with blood transfusions (Bolton-Maggs 2014; Vamvakas 2007). The limited supply and increasing cost of blood has placed additional emphasis on appropriate transfusion practice (Murphy 2011; Shander 2011).

Description of the intervention

Marked progress has been made on developing strategies for RBC transfusion. For many years, based on the findings of Adam 1942, RBC transfusion was recommended when the haemoglobin level dropped below 100 g/L or the haematocrit was below 30%. Although originally recommended to improve outcomes in people undergoing surgery with poor anaesthetic risk, this perioperative threshold was adopted in many other areas of clinical practice. This was challenged by the Transfusion Requirements In Critical Care (TRICC) trial, a landmark randomised controlled trial (RCT) that assessed the rates of death and severity of organ dysfunction using restrictive versus liberal transfusion strategies in the critical care setting (Hébert 1999). The restrictive strategy was to maintain the haemoglobin between 70 g/L to 90 g/L with a trigger for transfusion when the haemoglobin dropped below 70 g/L, whereas the liberal transfusion strategy was to maintain the haemoglobin between the range of 100 g/L to 120 g/L, with a threshold for transfusion when the haemoglobin dropped below 100 g/L. The restrictive transfusion strategy was seen to be as safe as the liberal transfusion strategy with similar 30-day overall mortality rates. In a recent systematic review that assessed a restrictive versus liberal RBC transfusion strategies (31 trials, 9813 participants), the restrictive strategy was associated with a reduction in the number of RBC units transfused, with no differences in mortality and overall morbidity compared to a liberal strategy (Holst 2016). Moreover, results from a Cochrane review (19 trials, 6264 participants) also highlighted that restrictive transfusion strategies are safe, with no impact on mortality, cardiac events, myocardial infarction, stroke, pneumonia and thromboembolism when compared with liberal strategies (Carson 2016).
The current NICE guidelines recommend implementing restrictive RBC transfusion thresholds of a haemoglobin level after transfusion of between 70 g/L to 90 g/L, when major haemorrhage, acute coronary syndrome and chronic anaemia are absent (NICE 2015). In addition, the transfusion of a single RBC unit is also recommended for adults who do not have active bleeding.
Carson 2016 indicated that on average, restrictive transfusion strategies reduced the risk of receiving a transfusion by 39% compared to the liberal transfusion strategy. Similar findings were also seen from a retrospective cohort study in 139 people with haematological malignancies receiving intensive chemotherapy, this also Implementing a single-unit transfusion policy that saved 25% of RBC units and, in addition to reducing the risks associated with allogeneic blood transfusions (Berger 2012).
People receiving intensive therapy for haematological malignancy have different physiological requirements to the critical care population as they are generally more physically active as well as experiencing more profound periods of erythropoietic suppression. Great uncertainty remains about whether it is safe to 'withhold' blood for patients with haematological malignancy until a lower threshold level is reached, and about the impact this poses on mortality, bleeding and adverse events, in addition to quality of life (Valeri 1998).

How the intervention might work

The aim of RBC transfusion is generally to improve oxygen delivery to the organs - which could minimise morbidity, improve anaemia symptoms and enhance quality of life. However, unnecessary and unsafe blood transfusion practices could expose recipients to the risk of serious adverse transfusion reactions and TTI (WHO 2015).
The traditional transfusion threshold is a haemoglobin level of 100 g/L. This level has been lowered to haemoglobin levels between

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60 g/L to 80 g/L. The Transfusion Requirement in Critical Care (TRICC) trial was the first to suggest that a 70 g/L was a safe threshold and perhaps safer than the traditional 100 g/L threshold (Hébert 1999). Several later trials assessed transfusion strategies in different clinical areas concluding that a restrictive transfusion strategy would trigger transfusion of a certain number of RBC units below a defined haemoglobin concentration (Carson 2011; Colomo 2008; Hajjar 2010). A liberal transfusion strategy would adopt a higher haemoglobin threshold and patients would tend to receive more blood components. However, the liberal transfusion strategy is still in use, especially when treating coronary artery syndromes (Carson 2013). A Cochrane review on this topic including 19 RCTs with over 6000 trial participants enrolled from many different clinical settings - mainly surgical, trauma and critical care (Carson 2016) - concluded that restrictive transfusion strategies did not appear to impact the rate of adverse events or the 30-day mortality compared to liberal transfusion strategies. It was actually associated with a significant decline in hospital mortality.

In the recent systematic review on this topic (Holst 2016), only one RCT specifically included people with haematological malignancies. This study recruited 60 people with leukaemia undergoing chemotherapy or HSCT (Webert 2008). This multicentre, single-blinded pilot RCT assessed the feasibility of a larger trial to identify the effect of the haemoglobin concentration on bleeding risk using higher transfusion thresholds and determined that a larger RCT was feasible.

Why it is important to do this review

Both anaemia and transfusion are associated with increased morbidity and mortality and national clinical guidelines on the appropriate use of blood transfusion and systems to monitor its safety are not currently in place throughout the world (WHO 2015). The optimal RBC transfusion strategy remains unclear in patients with haematological malignancy receiving intensive treatment. Due to the lack of available good quality evidence, no clear transfusion strategies are recommended in national guidelines for haematology patients or for those receiving chemotherapy (Carson 2012; Gunn 2012; McCelland 2010). Therefore, great variability exists at a local level. In Canada, the majority of centres have adopted a transfusion trigger of 80 g/L with a general reluctance to use a lower trigger of 70 g/L in all but one of 15 centres surveyed (Tay 2011). In the UK, a national audit also showed great variability in practice (Tinegate 2016).

In a variety of patient populations, including critical care patients, RBC transfusions have been associated with increased mortality and morbidity including more frequent infections, poor wound healing and increased arterial and venous thrombotic events (Blajchman 2005; Hébert 1999; Khorana 2008). The accumulated evidence showed restrictive RBC transfusion could improve outcomes for critically ill people (Salpeter 2014), or people with acute upper gastro-intestinal bleeding (Villanueva 2013). Therefore, there is growing evidence to suggest that a restrictive RBC transfusion strategy is more beneficial than the liberal strategy in many clinical situations. However, this has not been systematically addressed in people with haematological malignancies.

A low haemoglobin level has been associated with an increased bleeding time (Ho 1998; Valeri 1998), and RBC transfusions have been shown to improve haemostasis in people with anaemia who are thrombocytopenic (Ho 1996) or uraemic (Livio 1982). Therefore, in people with haematological malignancies, a restrictive RBC transfusion policy may increase their risk of bleeding further in addition to their increased risk due to thrombocytopenia.

OBJECTIVES

To determine the efficacy and safety of restrictive versus liberal red blood cell (RBC) transfusion strategies for people diagnosed with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell transplantation (HSCT).

METHODS

Criteria for considering studies for this review

Types of studies

As it was likely that the number of randomised controlled trials (RCTs) that could be included in this review were small given the authors' tacit knowledge of the subject, we included data from non-randomised studies (NRS) for all outcome evaluations. We only included NRS which were prospective in design and included a rigorous definition of the interventions and outcomes measured as an attempt to assess as wide a data volume as possible. Such studies included quasi-randomised, non-RCTs and prospective cohort studies. We excluded retrospective and uncontrolled studies (e.g. case series) due to the potential for unacceptable bias. Despite the inferiority of study quality that most NRS offered, a review of eligible NRS might identify a need for further RCTs and prove informative to the design of such a trial.

Types of participants

We included studies conducted on people with haematological malignancies requiring a red blood cell (RBC) transfusion whilst receiving intensive chemotherapy or radiotherapy, or both, with or without HSCT. We Included studies on participants of all ages, with the exception of neonates (up to 28 days old). We accepted the

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individual study's definition of intensive chemotherapy or radiotherapy, sufficient to cause myelosuppression. The number of potential intensive chemotherapy or radiotherapy regimens, or both was broad. We listed some examples, but these were not limited to, chemotherapeutic regimes listed on public oncology web sites such as:

- Public Health England, Systemic anti-cancer therapy Chemotherapy Dataset;
- Cancer Care Ontario Drug Formulary;
- Macmillan Cancer Support Combination Chemotherapy Regimen;
- BC Cancer Agency Lymphoma and Myeloma Chemotherapy Protocols;
- Royal Surrey County Hospital NHS Foundation Trust Haematology Chemotherapy.

We included studies that involved participants at all stages of treatment. We included studies on people with high risk myelodysplasia (refractory anaemia with excess of blasts (RAEB), and RAEB in transformation into acute leukaemia, (RAEB-t)) if intensive chemotherapy or radiotherapy, or both was received. We excluded studies on people with a haematological malignancy requiring transfusion support only.

Where a study included mixed populations of participants, we planned to only use data relevant to haematological malignancies. There were no studies with mixed populations of participants with haematological and solid tumours or non-intensive and intensive chemotherapy. In future updates of this review, when a study includes mixed populations of participants with haematological and solid tumours, we will only use data relevant to haematological malignancies. If the data are not available within the published literature or through direct author contact, we will exclude the study if fewer than 80% of the study population had haematological malignancies or high-risk myelodysplasia. In future updates of this review, when studies include participants receiving intensive and non-intensive chemotherapy or radiotherapy for haematological malignancies, we will only include data from the former group. If these data are not available, we will exclude the study if fewer than 80% of the study population were receiving intensive chemotherapy or radiotherapy for haematological malignancies.

Types of interventions

We included allogeneic red blood cell (RBC) transfusion strategies defined as 'restrictive' and 'liberal'. We expected that such definitions varied between studies, however, we accepted the individual study definitions of these strategies such that the restrictive (intervention) group in all included studies should receive a transfusion of allogeneic RBC units below a certain 'trigger' or 'threshold' haemoglobin or haematocrit level. The control group should receive a transfusion of RBC in accordance with a more liberal transfusion policy such as when a higher haemoglobin or haematocrit threshold was reached. For the purposes of this Cochrane review, we applied a standard published equation to convert haematocrit to haemoglobin: Haemoglobin (g/dL) = Haematocrit (%)/3 (Quintó 2006).

Types of outcome measures

We reported the outcomes from RCTs and NRS separately (Reeves 2011).

Primary outcomes

All-cause mortality: all deaths (undefined time period); deaths during a defined period: short- (zero to seven days), medium- (eight to 30 days), and long-term intervals (31 to 100 days) where day zero is the start of the follow-up period or randomisation, or both.

Secondary outcomes

Mortality

- Deaths due to:
  - Infection;
  - Bleeding;
  - Adverse transfusion reactions.
- Death within 30 days of receiving:
  - Intensive radiotherapy;
  - Intensive chemotherapy;
  - HSCT.

Adverse events

- Bleeding episodes
  - Any bleeding (e.g. World Health Organization (WHO) grades 1 to 4, National Cancer Institute's common terminology criteria for adverse events (CTCAE 2009), grades 1 to 5 or equivalent)
  - Clinically significant bleeding (e.g. WHO/CTCAE grades $\geq$ 2 or equivalent)
  - Severe bleeding (e.g. WHO/CTCAE grade $\geq$ 3 or equivalent)
- Adverse transfusion reactions (e.g. TRALI, TACO, ABO incompatibility, TTI)
- Serious infections (e.g. CTCAE $\geq$ grade 3 or equivalent (CTCAE 2009))
- Arterial or venous thromboembolic events
- Toxicity score for HSCT recipients (e.g. Bearman Toxicity Score $\geq$ grade 3 or equivalent (Bearman 1988))

Blood product requirements

- RBC transfusion requirements and intervals
- Platelet transfusion requirements and intervals

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Other

- Quality of life
- Length of hospital admission
- Length of intensive care admission
- Hospital readmission

We tried to report secondary outcomes over meaningful periods common to as many studies as possible, such as the number and severity of bleeding episodes per person per day of study.

Search methods for identification of studies

The Information Specialist of the Systematic Review Initiative (CD) formulated the search strategies in collaboration with the Cochrane Haematological Malignancies Group. The searches for this review were performed in to phases the first phase was run until December 2012, thereafter the second phase was run until November 2015.

Electronic searches

Bibliographic databases

We searched for RCTs and NRS in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library 2016, Issue 6 -Appendix 1);
- MEDLINE (1946 to 15 June 2016- Appendix 2);
- Embase (1974 to 15 June 2016 - Appendix 3);
- CINAHL (1982 to 15 June 2016 - Appendix 4);
- PubMed (epublications only - Appendix 5);
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to 15 June 2016 - Appendix 6);
- LILACS (1982 to 15 June 2016 - Appendix 7);
- IndMed (1986 to 15 June 2016 - Appendix 8);
- KoreaMed (1995 to 15 June 2016 - Appendix 9);
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 15 June 2016 - Appendix 10).

We combined searches in MEDLINE with the Cochrane RCT highly sensitive search filter, as detailed in Lefebvre 2011 and with the SIGN observational studies filter for MEDLINE. Also, we merged searches in Embase and CINAHL with the relevant SIGN RCT and observational studies filters (www.sign.ac.uk/methodology/filters.html).

Ongoing studies databases

We also checked for ongoing RCTs and NRS in the following databases to 15 June 2016:

- ClinicalTrials.gov (Appendix 11);
- ISRCTN Register (Appendix 12);
- WHO International Clinical Trials Registry (ICTRP) (Appendix 13);
- EU Clinical Trials Register (EUDRACT) (Appendix 14).

Searches were not limited by date, language or publication status.

Searching other resources

We augmented database searching with the following.

Handsearching reference lists

We checked the reference lists of all included studies, relevant reviews, conference abstracts and current treatment guidelines to identify additional studies that were not retrieved through databases searches.

Personal contact

We contacted the lead authors of relevant studies, study groups and international experts working in this field to identify any unpublished material, or to gather information regarding ongoing studies.

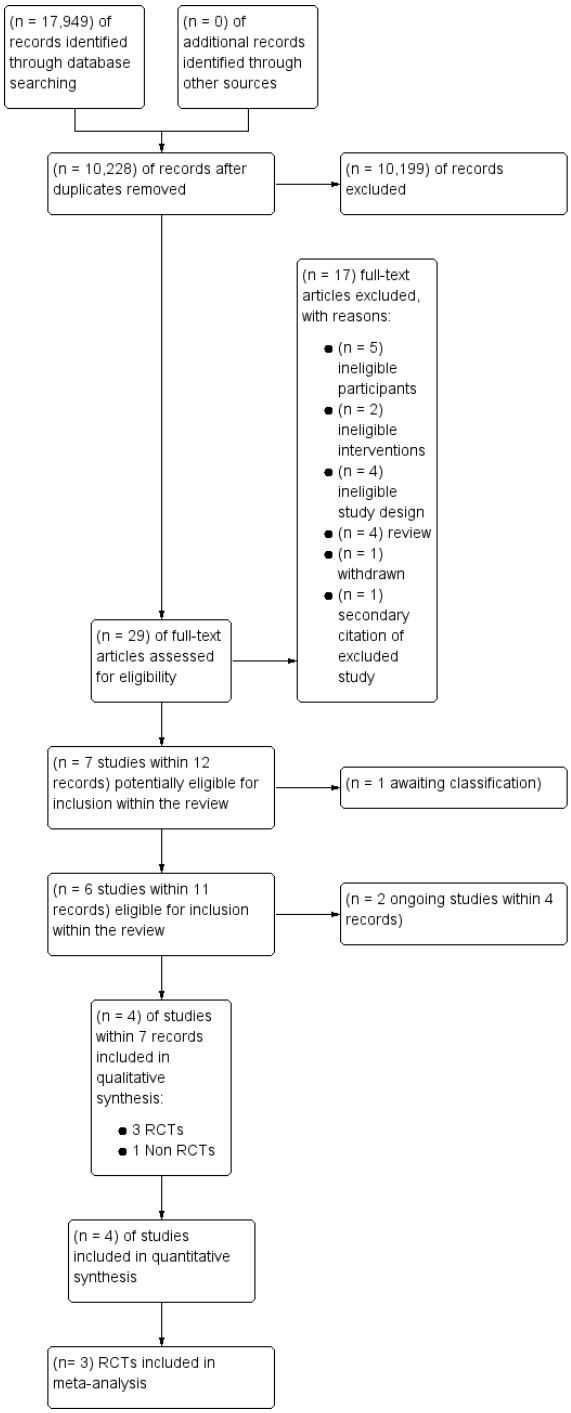
Data collection and analysis

Selection of studies

We selected studies according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) initially screened all search hits for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, two review authors (LE, RM) independently screened all the remaining references for relevance against the full eligibility criteria. We retrieved full-text papers for all references for which a decision on eligibility could not be made from title and abstract alone. We assessed study design features against the review inclusion criteria. Additional information was requested from study authors as necessary to assess the eligibility for inclusion of individual studies. Two review authors (LE, RM) discussed the results of study selection and resolved all disagreements by discussion without the need to consult a third review author (MM). We recorded the reasons why potentially relevant studies failed to meet the eligibility criteria. We reported the results of study selection using a PRISMA flow diagram (Moher 2009) (Figure 1).

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Figure 1. Study flow diagram for study selection



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We initially assessed the RCTs. As there were not two or more well-conducted eligible RCTs including at least 1000 patients, we extended the assessment and selection of studies to NRS.

Data extraction and management

As recommended in Higgins 2011a, two review authors (RM, LE) independently extracted data onto standardised forms and performed a cross-check. The two review authors piloted the data extraction form for included RCTs and NRS. Any disagreements between the review authors were resolved by consensus. We were not blinded to the names of the study authors, institutions, journals or the study outcomes. If a trial had multiple publications we used one form only to extracted relevant data. When these sources provided insufficient information, we contacted the authors and study groups for additional details. One review author (RM) performed data entry into software, which a second review author (LE) checked for accuracy.

We extracted the following information for each study:

1. Source: Study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details;
2. Eligibility: Fate of study; reason for exclusion (as appropriate);
3. General study information: Publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed;
4. Study design: Was there a comparison; how were participants allocated to groups?; which part of the study were prospective?; on which variables was comparability between groups assessed?; type of study;
5. 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); concerns regarding bias; inclusion & exclusion criteria; primary outcome(s); secondary outcomes;
6. Characteristics of interventions: Number of study arms; description of experimental arm; description of control arm; duration of red cell storage; frequency of minor ABO mismatched transfusions; other treatment (e.g. gamma irradiation);
7. Characteristics of participants: Age; gender; ethnicity; body surface area; primary diagnosis; stage of disease; category of intensive chemotherapy received; details of radiotherapy received; type of HSCT received; additional therapy received; risk of alloimmunisation; baseline haematology laboratory; subgroups evaluated; cofounders reported;
8. Participant flow: Total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for primary outcome); number of allocated patients who received planned treatment; number of drop-outs with reasons (percentage in each arm); protocol violations; missing data;
9. Outcomes: All cause mortality (undefined and within short, medium and long term periods); mortality due to infection, bleeding, TRALI, TACO, ABO incompatibility, TTI, other (with details); number and severity of bleeding episodes, adverse transfusion reactions, serious infections, toxicity score and quality of life scores; 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; duration of hospital admission; duration of intensive care admission; readmission to hospital during follow-up period.
10. In the case of the NRS, we additionally extracted information on confounding factors, results from adjusted models and variables adjusted for.

Assessment of risk of bias in included studies

We assessed the quality of all included trials (RCTs) using the Cochrane risk of bias tool as described in Higgins 2011b. Two review authors (RM, LE) independently assessed each element of potential bias listed below as either 'high', 'low' or 'unclear risk of bias'. We also provided a brief description in the Characteristics of included studies table of the judgement statements upon which the review authors assessed potential bias. We reached a consensus on the degree of risk of bias through comparison of the review authors' statements and, where necessary, through consultation with a third author (SH).

To assess risk of bias, we addressed the following questions in the 'Risk of bias' table for each included study.

- Selection bias: Was the allocation sequence randomly generated? Was allocation adequately concealed prior to assignment?
- Performance bias: Where possible, were the study participants and personnel adequately blinded?
- Detection bias: Was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?
- Attrition bias: Were incomplete outcome data adequately addressed for every outcome?
- Reporting bias: Are reports of the study free of selective outcome reporting?
- Other issues: Was the study apparently free of other problems that could put it at risk?

We assessed the quality of the NRS using an adapted Newcastle-Ottawa scale (Wells 2013). We included an expansion of the comparability of cohorts section with the inclusion of

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a list of important confounding factors we felt should be addressed in the studies methods or analysis. Also, we included an additional question concerning equal follow-up durations for mortality, the primary and secondary outcomes of this review. We scored the studies with reference to the Ottawa Hospital Research Institute's coding manual and scale guidelines. We provided judgement statements for each score in tabular form as for the 'Risk of bias' assessment of interventional trials. The score was reported out of a maximum of 10 stars using the following categories.

Selection (one star each, maximum four stars).

- Representiveness of the exposed cohort
- Selection of the non-exposed cohort
- Ascertainment of exposure
- Demonstration that outcome of interest was not present at start of study

Comparability (maximum of two stars).

- Recognition of at least 75% of the main potential confounding factors as listed below within study design or adjustment in analysis (two stars).

    - Primary diagnosis, separated by: haematological malignancy (acute leukaemia, high risk myelodysplasia, chronic lymphocytic leukaemia (CLL), myeloma, lymphoma) or natural history of primary diagnosis e.g. a) 'Indolent' (myeloma, low grade lymphoproliferative disorders (e.g. CLL, low grade lymphoma), acute lymphoblastic leukaemia/acute myeloid leukaemia in complete remission (CR1), chronic myeloid leukaemia in chronic phase, high risk myelodysplastic syndrome) or b) 'aggressive' (high grade lymphomas (e.g. diffuse large B-cell lymphoma (DLBCL), Burkitt), all other stages of acute leukaemia, chronic myeloid leukaemia in accelerated or blast phase).
    - Age: variability in the age of patients included, e.g. paediatric (< 18 years) versus adult ($\geq$ 18 years).
    - Gender: male to female ratio.
    - Previous severe bleeding (e.g. WHO/CTCAE grade $\geq$ 3 or equivalent).
    - Use of anticoagulation during study.
    - Previous alloimmunisation.
    - Co-existing cardiovascular disease.
    - Performance Status (e.g. ECOG, KPS).
    - HSCT: autograft versus allograft (allograft source: sibling, matched unrelated, cord donation; conditioning type: myeloablative including total body irradiation versus reduced intensity conditioning); harvest type: peripheral blood stem cell versus bone marrow harvest); ABO compatibility; cytomegalovirus (CMV) compatibility, stem cell dose received.
    - Radiation use in addition to intensive chemotherapy.

- Recognition of 50% to 75% of the main potential confounding factors within study design or adjustment in analysis (one star).

Outcome (one star each, maximum of four stars).

- Assessment of outcome.
- Was follow-up long enough for outcomes to occur?
- Adequacy of follow-up of cohorts.
- Follow-up equal between groups for primary and secondary outcomes?

We requested additional information from study authors as necessary to address the quality of individual studies. Two review authors discussed the results of the study quality assessment and try to resolve any discrepancies between themselves.

We planned to use the 'Risk of bias' assessment to explore statistical heterogeneity in each included study and to perform sensitivity analyses, but no meta-analyses were performed. For both RCTs and NRS, we planned to exclude monocentric studies from a sensitivity analysis due to their higher likelihood of bias, but no meta-analyses were performed.

Measures of treatment effect

We did not combine data retrieved from RCTs and NRS in a single meta-analysis, but reported data separately (Reeves 2011).

We undertook quantitative assessments using Review Manager (RevMan) 2014.

Randomised controlled trials (RCTs)

For dichotomous outcomes, we recorded the number of outcomes in the treatment and control groups and estimated the treatment effect measures across individual studies as the relative effect measures (risk ratio with 95% confidence intervals (CIs)). Where the number of observed events was small (< 5% of sample per group), we used Peto odds ratio (Peto OR) method for analysis (Deeks 2011). For continuous outcomes using the same scale, we assessed the mean difference (MD) with 95% confidence intervals (CI), and continuous outcomes measured with different scales we planned to present the standard mean difference (SMD). No hazard ratios (HR) 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).

Non-randomised studies (NRS)

For the NRS, we planned to report the adjusted odds ratios (OR) with 95% confidence intervals (CIs), but none were reported. If the adjusted ORs were not available, we planned to make every effort before pooling to establish whether the groups were comparable at base-line. No meta-analyses were performed, we planned to use the random-effects model for all analyses of NRS.

We were aware that after collecting the data and assessing the quality of the included studies, it might be necessary to alter the analysis plan based on methodological considerations. No changes were made because we only included one NRS.

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All studies

We did not report the number needed to treat to benefit (NNTB) with CIs and the number needed to treat to harm (NNTH) with CIs because there were no differences between any of the outcomes.

If we could not report the available data in any of the formats described above, we performed a narrative report.

Unit of analysis issues

There were no cluster-randomised trials or cross-over studies eligible for inclusion in this review.

We treated other unit of analysis issues in accordance with the advice given in Higgins 2011c. There was a unit of analysis issue for this review for the number of RBC or platelet transfusions reported in Webert 2008. Data were reported per participant day rather than per participant. However, the authors used a recurrent events analysis to take into account the repeated events data (Cook 1997).

Dealing with missing data

Where we identified data as missing or unclear in published literature, we contacted study authors directly. We recorded the number of patients lost to follow-up for each study. Where possible, we planned to analyse data by intention-to-treat (ITT) but if insufficient data were available, we planned to present per protocol (PP) analyses (Higgins 2011c).

Assessment of heterogeneity

We only performed one meta-analysis due to the small number of eligible studies and the lack of studies reporting similar outcomes. We had planned to perform separate meta-analyses for data extracted from RCTs and observational studies, if the clinical and methodological characteristics of studies were sufficiently homogeneous. We had also planned to assess the statistical heterogeneity of treatment effects between pooled studies using a Chi^2 test with a significance level at $P < 0.1$. We would have used the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if $I^2 > 30\%$ or considerable if $I^2 > 75\%$.

We also anticipated that there would be at least moderate clinical and methodological heterogeneity within the included studies and the random-effects model would be appropriate. If the heterogeneity was still considerable, we also planned to not report the overall summary statistic. In addition, we planned to assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias (small-trial bias) (Sterne 2011), because the review included fewer than 10 trials.

Data synthesis

We performed analyses according to the recommendations of Deeks 2011 using aggregated data for analysis. For statistical analysis, we entered data into the Cochrane statistical package of Review Manager (RevMan) 2014. One review author (RM) entered the data into the software. A second author (LE) checked data for accuracy. We were only able to perform a limited number of meta-analyses due to the small number of eligible studies and the perceived clinical and methodological heterogeneity between these studies. Aditionally, we provided a narrative quantitative summary for relevant outcome data retrieved from RCTs and NRS separately. If the qualitative assessment was not feasible, we therefore described outcome data extracted from each study individually and we also commented on any apparent trends.

We used the GRADE system to build a 'Summary of Findings' table, as suggested in Schünemann 2011a and Schünemann 2011b. In the review protocol we considered the following most relevant outcomes.

- All-cause mortality
- Quality of life
- Bleeding episodes
- Serious infections
- Length of hospital admission
- Hospital readmission rate

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were performed because we only performed a limited number of meta-analyses. We had planned to perform subgroup analysis for each outcome if data were available for the following.

- Intensive chemotherapy versus radiotherapy.
- Paediatric (less than 18 years) versus adult (18 years or older).
- HSCT versus no HSCT.
- For those that received HSCT:
    - autologous HSCT versus allogeneic HSCT;
    - reduced intensity transplant versus myeloablative HSCT.
- For those that received intensive chemotherapy without HSCT:
    - induction versus consolidation chemotherapy (at least for acute leukaemia);
    - acute leukaemia versus non acute leukaemia.

We had also planned to undertake a subgroup analysis of results from studies including participants with pre-existing cardiovascular diseases, if the relevant data were given separately in the study.

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Sensitivity analysis

This was not feasible as we only performed a limited number of meta-analyses and one of which was where data from the three included RCTs were combined. However, we originally 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' (e.g. 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% dropout rate;
- including only multicentric studies.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification and Characteristics of ongoing studies.

Results of the search

See the PRISMA Flow Diagram (Figure 1). We identified a total of 17,949 potentially-relevant records in the search conducted on 15 June 2016. There were 10,228 records after we removed duplicates. Two out of four reviewers (CB, LE, RM, JT) excluded 10,199 records on the basis of the abstract (two were review authors and two were protocol authors). The full texts of 29 articles were assessed for eligibility. Of those, 16 studies within 17 records were excluded with reasons; details were listed in the Characteristics of excluded studies table. We identified seven studies, within 12 records that met or may meet the review inclusion criteria. One of these is awaiting classification (NCT02099669), two of these are ongoing studies (Chantepie 2015; Tay 2011), three were randomised controlled trials (RCTs) (Robitaille 2013; Webert 2008; De Zern 2016) and one was a prospective non-randomised study (NRS) (Jansen 2004).

We contacted the author of one potentially eligible for inclusion study (Mear 2014), as the study was only available as an abstract. We requested additional information related to the study design, study detailed data and whether the study authors were aware of any relevant ongoing or completed studies. The authors provided us with the requested information and thereafter we excluded the study as data were collected retrospectively.

We did not find any additional studies from other sources: checking lists of reference from the included studies and relevant reviews or by contacting experts in the field. All included studies were published in English.

Included studies

See Characteristics of included studies for full details of each study. The four studies eligible for inclusion in this review were conducted between 1997 and 2015 and published between 2004 and 2016.

Three were RCTs, two were conducted in Canada (Robitaille 2013; Webert 2008), and one (De Zern 2016), in the USA. The remaining study was an NRS (Jansen 2004) conducted in the Netherlands.

Description of included RCTs

Study design and duration

We included three RCTs in this review, two were planned to be multicentre parallel RCTs (Robitaille 2013; Webert 2008) and De Zern 2016 was a single-centre trial. Robitaille 2013 planned to recruit participants from six centres, however only one centre recruited participants prior to the trial's closure by the Data Safety Monitoring Board (DSMB). Two RCTs were open-label trials (Robitaille 2013; De Zern 2016) and the other one was a single-blinded trial (Webert 2008). Robitaille 2013 was closed after recruiting six participants because all three participants in the liberal transfusion arm were diagnosed with veno-occlusive disease (VOD). The DSMB made their decision based on clinical observations, statistical comparison of the data in the two study arms, and statistical comparison of the data in the liberal transfusion arm with historical (non-trial) data that used a restrictive threshold.

In Webert 2008, the mean follow-up period was 25.9 days (standard deviation (SD), 8.4) in the restrictive group and 23.6 days (SD, 10.0) in the liberal group for a total of 1482 days of observation. In Robitaille 2013, all participants were followed up until day +100 from randomisation and in De Zern 2016, both groups had a similar follow-up time, the median duration was 5.6 weeks for participants in the restrictive group and 6.1 weeks for the liberal group.

Study size and setting

The number of participants recruited ranged from six (Robitaille 2013) to 90 (De Zern 2016). In Robitaille 2013, the six participants were recruited from paediatric transplant centres, and in both Webert 2008 and De Zern 2016, 150 participants were inpatients recruited from tertiary referral haematology centres.

Two trials were conducted in Canada (Robitaille 2013; Webert 2008) and the third (De Zern 2016) was conducted in the USA. The studies were conducted between 2000 and 2015.

Study participants

In total, 156 participants were randomised, and 155 were included in the analyses, one participant withdrew from the De Zern 2016

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study prior to any study transfusion. One hundred and fifty participants were adults: 134 with acute leukaemia receiving chemotherapy, and 16 with a haematological malignancy receiving an allogeneic stem cell transplant (De Zern 2016; Webert 2008). Six were children (mean age 11.7 years): three with acute myeloid leukaemia, two with myelodysplasia, and one with immune deficiency; all children received an allogeneic bone marrow transplant (Robitaille 2013).

In Webert 2008, there was no significant difference in the baseline haemoglobin level between the two groups (restrictive: 96.3 g/L, liberal: 96.5 g/L, P = 0.96), in De Zern 2016, the baseline haemoglobin levels were significantly lower in the restrictive group (restrictive: median 83 g/L, liberal: median 89 g/L, P = 0.03) . The baseline haemoglobin levels were not reported in Robitaille 2013.

Participants with active bleeding were included in Robitaille 2013, however they were excluded in both Webert 2008 and De Zern 2016.

Participants with a history of cardiovascular disease were included in Robitaille 2013, excluded in Webert 2008, and only participants with acute coronary syndrome were excluded in De Zern 2016.

Study Interventions

The restrictive red blood cell (RBC) transfusion trigger thresholds varied between the three studies (70 g/L in Robitaille 2013 and De Zern 2016) and 80 g/L in Webert 2008).

The liberal RBC transfusion trigger threshold was the same in two RCTs (120 g/L) (Webert 2008; Robitaille 2013), and it was much lower at 80g/L in De Zern 2016.

The amount of RBC components transfused in each study arm were the same if a transfusion was required (10 mL/kg to 15 mL/kg) in Robitaille 2013; and two units of RBC components in Webert 2008 and De Zern 2016.

One trial reported the mean length of RBC component storage and this did not differ between the two groups (Robitaille 2013).

All trials reported off-protocol RBC transfusions. In Webert 2008, about a third of RBC transfusions were given in the restrictive group and liberal group when the haemoglobin level was above the study thresholds. In De Zern 2016, there were two off-protocol deviations, one participant in each trial arm received a blood transfusion above the study haemoglobin thresholds. In Robitaille 2013, protocol deviations were recorded and none of the participants received off-protocol transfusions.

In two trials (Robitaille 2013; Webert 2008), prophylactic platelets transfusions were given when the platelet count fell below 10 x 10^9/L. In Robitaille 2013, the platelet count threshold was increased to 20 x 10^9/L when infection or fever occurred, in Webert 2008 this depended on the protocol of the treating institution or physician. No information on when a platelet transfusion was given to participants was provided by De Zern 2016.

All other chemotherapeutic and other interventions were performed according to standard treatment protocols.

Study outcomes

In Webert 2008, no single primary ocutome was prioritised and all five determined outcomes were considered equally important for the study feasibility, these included: bleeding; proportions of days of thrombocytopenia; usage of RBC and platelet components and blood donor exposure, bleeding symptoms and severity.

In Robitaille 2013, time to neutrophil recovery was the study's primary outcome. Secondary outcomes included: time to platelet recovery, usage of RBC and platelet components, length of hospital stay, immune reconstitution, overall survival, transplant-related mortality, relapse, acute and chronic graft versus host disease (GvHD) and chimerism (Robitaille 2013). Several of these outcomes, including the planned primary outcome were not reported. The assessment of all long-term events was planned to be performed at one, two and five years follow-up.

In De Zern 2016, the safety and tolerability of a restrictive transfusion strategy in comparison with a liberal strategy was the primary outcome of the study. Secondary outcomes included fatigue, bleeding, response to therapy, vital status on day 60, length of hospital stay and the number of RBC units transfused, the number of platelets transfused per participant and the feasibility of conducting a larger RCT. Some outcomes were planned in the trial registration but not reported in the published paper, these were treatment-related mortality, end-organ dysfunction, number of participants with Eastern Cooperative Oncology Group (ECOG) < 2 performance status, the incidence of cross-over between the two groups due to symptomatic anaemia, and cost-effective analysis. All outcomes were planned to be assessed at day 60 from the trial onset.

Study funding

All three included trials were publicly funded; De Zern 2016 was sponsored by Sidney Kimmel Comprehensive Cancer Center; Robitaille 2013 was funded by Fonds de la Recherche en Sante (grant 9967 and 24460) and C17 research network and Webert 2008 was funded by Canadian Blood Services & CIHR Canada Research Chair.

Description of included NRS

Study design and duration

We included one NRS with prospective data collection, the mean follow-up period was 30 days for the restrictive group and 32 days for the liberal group (Jansen 2004). Data were collected as part of a previous RCT of chemotherapy agents in acute myeloid leukaemia.

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Study size and setting

Eighty-four participants were recruited from two inpatient haematology units within the department of haematology in Rotterdam (the Netherlands) from June 1997 to December 2001.

Study participants

Participants were aged 15 to 60 years with newly diagnosed acute myeloid leukaemia treated with induction chemotherapy (ARA-C and Idarubicin) . Participants were assigned to one of the following transfusion strategies based on where they were treated for their acute leukaemia. The two groups were comparable with no significant differences with regard to age, gender or French America British (FAB) classification of acute myeloid leukaemia. Participants with active bleeding were included, but participants with severe cardiac dysfunction were excluded.

Study intervention

Restrictive transfusion strategy: (age dependent): participants aged less than 25 years received a RBC transfusion when their haemoglobin was less than 72 g/L; participants aged 25 to 50 years received a RBC transfusion when their haemoglobin was less than 80 g/L; participants aged 50 to 70 received a RBC transfusion when their haemoglobin was less than 88 g/L. They received one unit of RBCs.
Liberal transfusion strategy: participants received a RBC transfusion when their when haemoglobin level was less than 96 g/L. They received two units of RBCs at each transfusion.
Off-protocol transfusion: No off-protocol transfusion was reported, though the plan was to always transfuse blood regardless of the haemoglobin readings when signs and symptoms of decreased oxygen transportation capacity occurred.

Study outcomes

The study's primary outcome measures were to show the differences of the total number of RBC transfusions and the number of units of RBCs given per transfusion between the two groups. Secondary outcomes included: mortality, bleeding, infections, cardiac arrhythmia and cardiac dysfunction, response to chemotherapy and the myeloid:erythroid ratio of the bone marrow smears.

Study funding

The initial RCT (HOVON 29 study) was partially funded by pharmaceutical companies.

Ongoing studies

We found two ongoing RCTs, published within three records, eligible for inclusion in this review (Chantepie 2015; Tay 2011). Both included ongoing studies are open-label parallel RCTs with two intervention groups. One is a single-centre RCT (Chantepie 2015) conducted in France and the second RCT is a multicentre Canadian RCT (Tay 2011). A total of 530 adult participants are planned to be recruited across the two ongoing trials by 2018. See Characteristics of ongoing studies.

Excluded studies

See Characteristics of excluded studies for further details. Reasons for exclusion were mainly involving non-haematological oncological participants, retrospective study design and reviews, and interventions that were not compatible with our inclusion criteria.

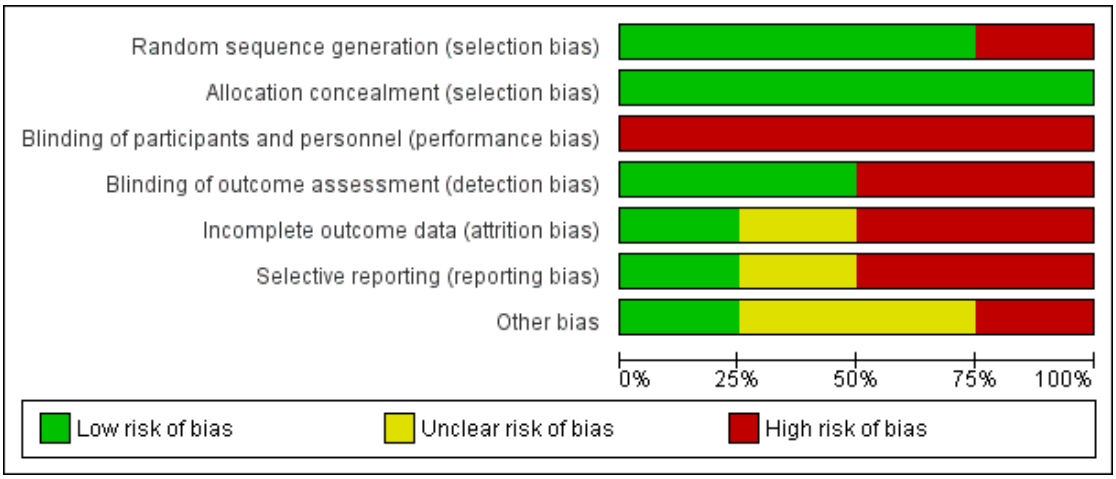
- Five studies were conducted on non-haematological participants (Almeida 2013; Bruun 2011; ISRCTN26088319; NTR2684; Yakymenko 2015).
- Five studies were not RCTs or NRS with no prospective design (Bercovitz 2011; Lightdale 2012; Mear 2014; Paananen 2009; Patil 2013).
- Two studies compared different interventions such as one versus two RBC units (Abels 1991; Berger 2012).
- Four records were reviews (Bercovitz 2011; Carson 2014; Holst 2013; Prescott 2016).

Risk of bias in included studies

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

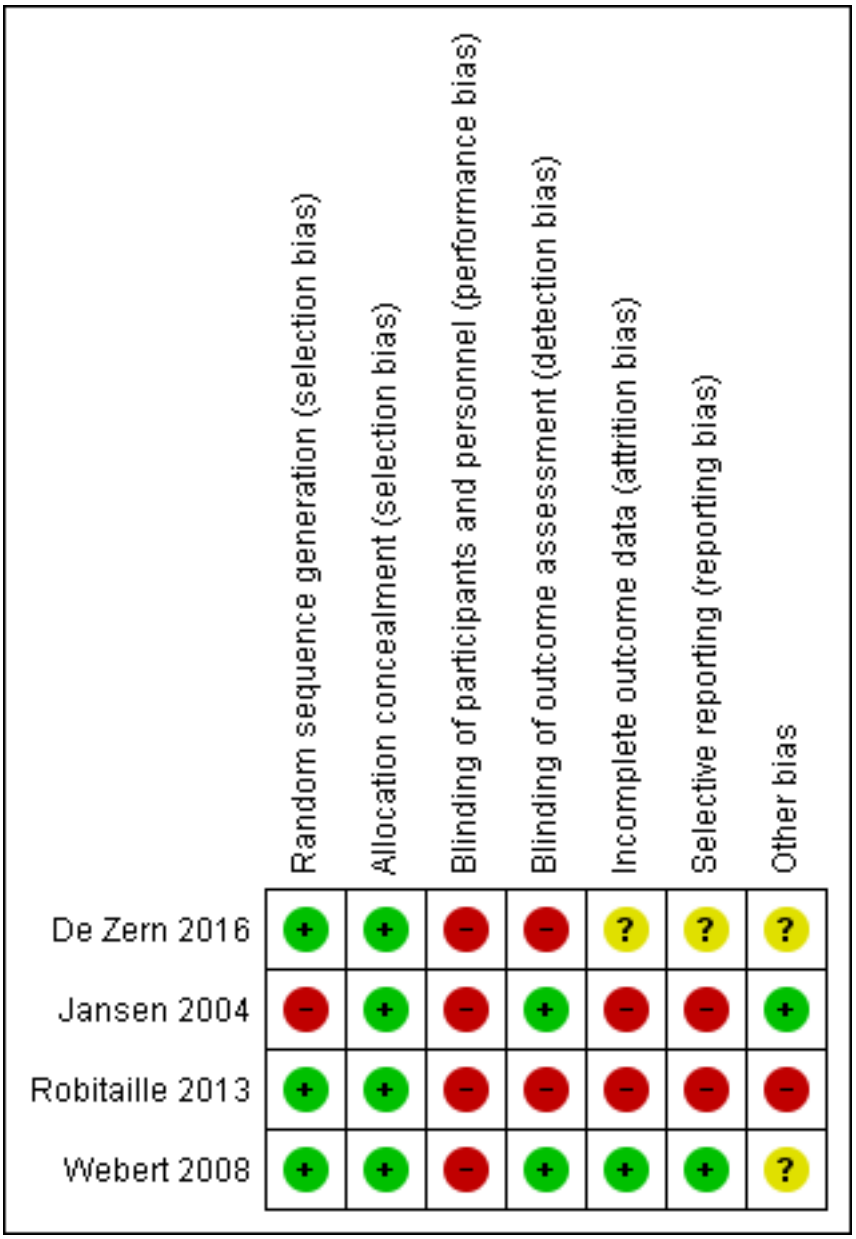
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Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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



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Risk of bias for included RCTs

Allocation

We assessed all three RCTS as low risk of selection bias due to adequate methods of sequence generation and allocation concealment.

Randomisation sequence generation:

All three trials provided information on method of randomisation. In Robitaille 2013 and De Zern 2016, randomisation was generated by computer and an Internet-based randomisation web site was used to assign participants to either intervention or control in Webert 2008. In Webert 2008, participants were stratified by their treatment centre and diagnosis, and treatment allocation was scheduled by using a computer-based generated random treatment allocation; this was developed with variable blocking factors and the size of the blocks selected randomly from a limited number of possibilities. In De Zern 2016, the random-number sequence was generated using computer software.

Allocation concealment:

All three trials provided an adequate description of allocation concealment. Two trials used a web-based randomisation system (Robitaille 2013; Webert 2008). One trial used sealed opaque sequentially numbered envelopes to allocate participants to either study arm (De Zern 2016).

Blinding

Blinding of participants and personnel:

We assessed all three trials as 'high risk' of performance bias. In Webert 2008, the study participants were aware of the intervention status and in both De Zern 2016 and Robitaille 2013 the study design was open-label.

Blinding of clinical assessors:

We assessed Webert 2008, as 'low risk" of detection bias, the personnel performing the clinical assessments were blinded to the participants' treatment allocation and to the haemoglobin levels.
We assessed De Zern 2016 and Robitaille 2013, as 'high risk" of detection bias, both trials were open-label design studies with no blinding.

Incomplete outcome data

We assessed one trial as 'low risk' of attrition bias (Webert 2008). All participants were accounted for within the study flow diagram and there were no withdrawals.
We assessed one trial as 'unclear risk' of attrition bias as the number of participants who withdrew from study was slightly higher from the restrictive group (De Zern 2016).
We assessed Robitaille 2013, as 'high risk' of attrition bias because all participants in the liberal transfusion arm were withdrawn from the study prior to day 100.

Selective reporting

We assessed Webert 2008 as 'low risk' of reporting bias as all study outcomes were prespecified by the authors and were provided for the study two groups.
We assessed De Zern 2016 as 'unclear risk' of reporting bias as some of the outcomes listed by the authors in the trial registration were not mentioned in the published paper. These outcomes were: mortality related to treatment, end-organ dysfunction, number of participants with Eastern Cooperative Oncology Group (ECOG) performance status < 2, the incidence of treatment cross-over because of symptomatic anaemia and cost-effective analysis of restrictive RBC transfusion. The authors responded to our request for clarification by stating these outcomes would be the subject of a second paper.
We assessed Robitaille 2013 as 'high risk' of reporting bias due to the early discontinuing of the study, many of the planned outcomes were not reported or their analysis was not performed.

Other potential sources of bias

We assessed two trials as 'unclear risk' of other bias (De Zern 2016; Webert 2008). In De Zern 2016, the baseline haemoglobin level was significantly lower in the restrictive group, the analysis was adjusted for baseline haemoglobin, and a risk of contamination between the two groups reported as some participants crossed over from the restrictive to the liberal group. The two groups in Webert 2008 were not totally comparable as the number of study days after reaching the target haemoglobin levels differed between the groups, and it took longer for the liberal group to reach the threshold.
We assessed Robitaille 2013 as 'high risk' of other bias because the study was stopped early due to an increase incidence of VOD and therefore may substantially overestimate the risk of harm associated with a liberal RBC transfusion strategy.

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Risk of bias for included NRS:

We used the Newcastle-Ottawa Quality assessment scale (a star rating tool of risk of bias in three broad areas: selection of cohort, comparability cohort and outcomes) to assess the risk of bias for the one included NRS (Jansen 2004) . Details are presented in Table 3.

Selection of cohort

We awarded two out of a possible four stars for selection of cohort, one for the ascertainment of exposure as this study was part of a randomised controlled trial (HOVON 29), and the second star was given because the outcomes of interest were prespecified. No stars were awarded for the representative of the exposed cohort; only participants with acute myeloid leukaemia were included. Additionally, the selection of the non-exposed cohort, was not clear with insufficient information to suggest that participants in the control group (non-exposed), were drawn from the same community as the exposed cohort.

Comparability of the cohort

We gave zero out of a possible two stars for comparability of the cohort because the multiple regression model only adjusted for gender, age and acute myeloid leukaemia type. There was no considerations to other possible confounders such as severe bleeding, use of anticoagulation, use of radiotherapy in addition to chemotherapy, cardiovascular disease, previous alloimmunisation or performance status.

Assessment of outcomes

We awarded two out of a possible four stars for assessment of outcomes, one for adequate follow-up time for the assessed outcomes and the second for the equal follow-up between the two groups for both primary and secondary outcomes. We did not give any stars for assessment of outcomes. Hence, no information was given whether the outcomes were assessed blindly, and whether the follow-up period was adequate. Some information was missing with regard to the incidence of infections, mean haemoglobin during follow-up, total number of platelets and RBC units received.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2** Summary of findings of NRS

We reported results from the three included RCTs and the one NRS individually in this review.

Effects of the interventions from included RCTs

Primary outcome: all-cause mortality

All-cause short-term mortality, within zero to seven days from the study start

One of the three included RCTs provided data for this outcome (Robitaille 2013). No deaths occurred in either treatment arm; all six participants were alive at seven days.

All-cause medium-term mortality, within eight to 30 days from the study start

One of the three included RCTs provided data for this outcome (Robitaille 2013). No deaths occurred in either treatment arm; all six participants were alive at 30 days.

All-cause long-term mortality, within (31 to 100 days) from the study start

Two of the three included RCTs provided data for this outcome (De Zern 2016; Robitaille 2013). No deaths occurred in one of the studies (Robitaille 2013), and in De Zern 2016 one death occurred in the restrictive group and two deaths in the liberal group. There was no evidence for a difference in the number of participants who died between a restrictive and liberal RBC transfusion strategy (two studies; 95 participants; risk ratio (RR) 0.25, 95% CI 0.02 to 2.69, P = 0.26) (*low-quality evidence*) (Analysis 1.1)

The small number of children enrolled in Robitaille 2013 were followed up for two years with one death occurred at six months from the liberal group due to relapse from leukaemia.

Secondary outcomes

Mortality

Deaths due to: infection; bleeding; adverse transfusion reactions

One of the three included RCTs reported: death due to infection; death due to bleeding or death due to transfusion reactions (Robitaille 2013). No deaths occurred in either treatment arm; all six participants were alive at 100 days.

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Deaths within 30 days of receiving: intensive radiotherapy; intensive chemotherapy; haematopoietic stem cell transplant (HSCT)

Death due to intensive radiotherapy
None of the three included RCTs looked at this outcome.
Death due to intensive chemotherapy
One of the three included RCTs reported death within 30 days of receiving intensive chemotherapy (De Zern 2016). We are very uncertain whether there is any difference in death due to intensive chemotherapy between the two groups (one study; 89 participants; RR 0.51, 95% CI 0.03 to 7.85) (Analysis 1.2).
Death due HSCT
One of the three included RCTs reported death within 30 days of receiving a HSCT (Robitaille 2013), no deaths occurred in either treatment arm; all six participants were alive at 30 days.

Adverse Events

Bleeding episodes

Bleeding was reported in two of the three studies (De Zern 2016; Webert 2008).

- Participants with any bleeding

There may be little or no difference in the number of participants who suffered from any bleeding between a restrictive versus liberal RBC transfusion strategies (two studies; 149 participants;RR 0.93, 95% CI 0.73 to 1.18, P = 0.54) (*low-quality evidence*) (Analysis 1.3).

- Clinically significant bleeding (WHO grade 2 and above)

There may be little or no difference in the number of participants who experienced clinically significant bleeding between the restrictive and liberal groups (two studies; 149 participants; RR: 1.03, 95% CI 0.75 to 1.43, P = 0.85) (*low-quality evidence*) (Analysis 1.4)

- Severe bleeding (WHO grade 3 and above)

We are very uncertain whether there is any difference between a restrictive versus liberal RBC transfusion strategies in the number of participants who suffered from severe bleeding (WHO grade 3 and above) (two studies; 149 participants; RR: 1.57, 95% CI 0.39 to 6.30) (Analysis 1.5) (Data from the Webert 2008 study was unpublished data provided by the study authors).
Webert 2008 also reported number of days with bleeding (RR: 1.19, 95%CI 0.84 to 1.70, P = 0.323) and time to first bleeding episode (RR: 1.36, 95%CI 0.79 to 2.34, P = 0.27) with no difference between treatment arms was seen. (Authors' own data).

Adverse transfusion reactions: such as transfusion-related acute lung injury (TRALI), transfusion-related circulatory overload (TACO), ABO incompatibility or transfusion transmitted infection (TTI)

None of the included trials provided data for these outcomes.

Serious infections

De Zern 2016 reported the episodes of neutropenic fever. We are very uncertain whether there is any difference in the number of participants who had experienced fever with positive blood culture between the restrictive and liberal transfusion strategy groups (one study; 89 participants; RR: 1.23, 95% CI 0.74 to 2.04) (*very low-quality evidence*) (Analysis 1.6) (unpublished data provided by the author).

Arterial or venous thromboembolic events

None of the included trials provided data for this outcome.

Toxicity score for HSCT recipients

No data were provided for a toxicity score from the two included RCTs that included HSCT recipients (Robitaille 2013; Webert 2008). However, Robitaille 2013, reported the occurrence of veno-occlusive disease (VOD) (a complication of HSCT). There was an increase in the risk of VOD in the liberal transfusion arm (Peto OR 28.03, 95% CI 1.51 to 520.65; six participants) (Analysis 1.7).

Blood product utilisation

Red blood cell (RBC) transfusion requirements and intervals

All three RCTs reported RBC transfusion requirements (Robitaille 2013; Webert 2008; De Zern 2016); no RCTs reported RBC transfusion intervals (see Table 4 for details).

- Number of participants who received a RBC transfusion

All three trials reported the number of participants who received a RBC transfusion (De Zern 2016; Robitaille 2013; Webert 2008). There may be little or no difference in the number of participants who required RBC transfusions from study entry between the restrictive and liberal RBC transfusion groups (three studies; 155 participants: RR: 0.97, 95% CI 0.90 to 1.05) (Analysis 1.8). However, in the Webert 2008 study there was a reduction in the number of participants who required RBC transfusions in the restrictive RBC transfusion group after the study haemoglobin threshold was reached (one study; 57 participants: RR: 0.83, 95% CI 0.70 to 0.99) (Analysis 1.9).

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- Number of RBC transfusions per participant

We calculated the mean number of RBC transfusions per participant based on individual patient data provided in the study report (Robitaille 2013) (Table 4). There was a reduction in the mean number of transfusions in the restrictive RBC transfusion group (two studies; 95 participants; mean difference (MD) -3.58, 95%CI -5.66 to -1.49, P < 0.0001) (Analysis 1.10).

- Proportion of participant days with a RBC transfusion

One trial reported the proportion of participant-days with a RBC transfusion.There was a reduction in the proportion of participant-days with a RBC transfusion in the restrictive RBC transfusion group from study entry ((Table 4). There was no evidence for a difference once the target haemoglobin levels were reached (Table 4).

Platelet transfusion requirements and intervals

Two trials provided data on platelet transfusion requirements (De Zern 2016; Webert 2008). See details in Table 5. No trials provided data on platelet transfusion intervals.

- Number of participants who received a platelet transfusion

There may be little or no difference in the number of participants who required platelets transfusions between the restrictive and liberal groups from study entry (one trial; 60 participants; RR: 1.03, 95% CI 0.86 to 1.24) (Analysis 1.11).

- Number of platelet transfusions per participant

In De Zern 2016, there may be little or no difference in the number of platelet transfusions per participant between the groups (restrictive group: median 9, Interquartile range (IQR) 5.5 to 12.5; liberal group: median 9, IQR 7 to 12) (Table 5) (Authors' own data).

- Proportion of participant days with a platelet transfusion

In Webert 2008, there may be little or no difference in the proportion of participant days with platelet transfusions between the restrictive and liberal groups from study entry, or after the study haemoglobin threshold was reached (Table 5) (Authors' own data).

Quality of life

One RCT reported quality of life (De Zern 2016), and a fatigue-self scoring tool was implemented (Mendoza 1999). This is a 10-point scale with a score of zero indicating no fatigue and a score of 10 indicating the worst possible fatigue. The median fatigue scare was similar for both groups; for restrictive group: 4.8 (IQR: 4 to 5.2) and for the liberal group: 4.5 (IQR: 3.6 to 5), P = 0.53 (Authors' own data).

Length of hospital admission

De Zern 2016 reported no difference in the length of hospital stay between the two groups; the median stay for restrictive group was 35.5 days (IQR; 31.2 to 43.8) compared with 36 days, IQR: 29.2 to 44, (P = 0.53) (Authors's own data).

Length of intensive care admission

None of the included RCTs measured this outcome.

Hospital readmission

None of the included RCTs measured this outcome.

Effects of the interventions from included NRS

All the following outcomes were reported from the one included NRS (Jansen 2004).

Primary outcome: all-cause-mortality

All-cause short-term mortality, within zero to seven days and eight to 30 days from the study start

The Jansen 2004 study did not report these outcomes.

All-cause long-term mortality, within (31 to 100 days) from the study start

The Jansen 2004 study reported this outcome.Two deaths occurred over a mean 31 days follow-up, one participant died from each group (*very low-quality evidence*). No adjusted analysis was reported.

Secondary outcomes

Mortality causes

Mortality: death due to infection; bleeding; or adverse transfusion reactions

Jansen 2004, did not report on any of these outcomes.

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Mortality within 30 days: due to intensive radiotherapy; or intensive chemotherapy

Jansen 2004, did not report on any of these outcomes.

Mortality within 30 days: due to HSCT

No participant in the Jansen 2004 study had a HSCT.

Adverse events

Bleeding episodes

- Participants with any bleeding

Jansen 2004, did not report the number of participants with any bleeding.

- Clinically significant bleeding (WHO grade 2 and above)

The authors did not report an adjusted analysis. Three participants had clinically significant bleeding in the restrictive group (38 participants) and eight participants had clinically significant bleeding in the liberal group (46 participants). The authors reported that there was no significant difference between the two groups.

- Severe bleeding (WHO grade 3 and above)

Jansen 2004, did not report the number of participants with severe bleeding.

Adverse transfusion reactions: such as transfusion-related acute lung injury (TRALI), transfusion-related circulatory overload (TACO), ABO incompatibility or transfusion transmitted infection (TTI)

Jansen 2004, did not report on adverse transfusion reactions.

Serious infections

In Jansen 2004, it was stated that "No differences were found in incidence of infections and type of infective agents" between the two transfusion strategies. However, no data were provided to support this.

Arterial or venous thromboembolic events

Jansen 2004, did not report on arterial or venous thrombosis incidence.

Toxicity score for HSCT recipients

No participant in the Jansen 2004 study had a HSCT.

Blood product utilisation

Red blood cell (RBC) requirements and intervals

- The total number of RBC transfusions was lower in the restrictive group compared to the liberal RBC transfusion group (unadjusted ratio of the geometric means 1.17, 95% CI 1.01 to 1.37: adjusted for age, sex and acute myeloid leukaemia type geometric mean 1.25; 95% CI 1.07 to 1.47 - data analysis performed by the study authors)
- The study authors stated that the number of RBC units given per transfusion was lower in the restrictive strategy group in comparison with the liberal strategy (Table 4). The study authors did not report an adjusted analysis.
- The mean interval between RBC transfusions was 3.1 days in the restrictive group compared to 3.0 days in the liberal group (Table 4). The study authors did not report an adjusted analysis.

Platelet requirements and intervals

- The study authors stated that there was no difference in the number of platelet transfusions per participant between the restrictive and liberal groups (Table 5). The study authors did not report an adjusted analysis.
- The study authors stated that there was no difference in the number of platelet units per participant between the restrictive and liberal groups (Table 5). The study authors did not report an adjusted analysis.
- The mean interval between platelets transfusions was 4.0 days in the restrictive group and 3.8 days in the liberal group (Table 5). The study authors did not report an adjusted analysis.

Other outcomes

Quality of life

This outcome was not assessed in Jansen 2004.

Length of hospital admission

This outcome was not assessed in Jansen 2004.

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Length of intensive care admission

This outcome was not assessed in Jansen 2004.

Hospital readmission

This outcome was not assessed in Jansen 2004.

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Restrictive compared with liberal for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Patient or population: people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support
Setting: Department of haematology
Intervention: Restrictive
Comparison: Liberal red blood cell transfusion NRS

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with liberal red blood cell transfusion RCTs	Risk with Restrictive			
All-cause mortality at 31 to 100 days	**Liberal:** 1 death (46 participants) **Restrictive**: 1 death (38 participants)		84 (1 study)	⊕◯◯◯ VERY LOW[1]	Mean 31 days follow-up
Quality of life - not reported	-	-	-	-	
Number of participants with any bleeding - not reported	-	-	-	-	
Number of participants with clinically significant bleeding	**Liberal:** 8 (46 participants) **Restrictive**: 3 (38 participants)		84 (1 study)	⊕◯◯◯ VERY LOW[1]	The study authors reported that there was no significant difference between the two groups
Serious infections - not reported	-	-	-	-	

Length of hospital admission - not reported	-	-	-	-
Hospital readmission rate - not reported	-	-	-	-

*__The risk in the intervention group__ (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]The level of evidence was downgraded by 1 due to imprecision.

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DISCUSSION

Our main objective of conducting such a review was to compare participants safety and clinical outcomes of a restrictive blood transfusion strategy and a liberal blood transfusion strategy for people with haematological disorders undergoing myelosuppressive chemotherapy or stem cell transplantation. In recent years, a more conservative blood transfusion policy had been implemented in other populations.

Summary of main results

We identified four studies for inclusion in this review, three randomised controlled trials (RCTs) and one non-randomised study (NRS) involving in total 240 participants.

We identified six studies eligible for inclusion in this review; five RCTs and one NRS. Three completed RCTs (156 participants), one completed NRS (84 participants), and two ongoing RCTs. The completed studies were conducted between 1997 and 2015. One study included children receiving a haematopoietic stem cell transplantation (HSCT) (six participants), the other three studies only included adults, 218 participants with acute leukaemia receiving chemotherapy, and 16 with a haematological malignancy receiving a HSCT. The restrictive strategies varied from 70 g/L to 90 g/L. The liberal strategies also varied from 80 g/L to 120 g/L. There is one additional study awaiting classification.

The follow-up time from randomisation to outcome reporting was short, four to six weeks, in three studies (De Zern 2016; Jansen 2004; Webert 2008). In Robitaille 2013, mortality was assessed at two years from the initial enrolment day.

Summary of main results from included RCTs

A restrictive red blood cell (RBC) transfusion policy may reduce the number of RBC transfusions per participant (two trials; 95 participants; mean difference (MD) -3.58, 95%CI -5.66 to -1.49).

A restrictive RBC transfusion policy may make little or no difference to:

- the number of participants who require RBC transfusions (three trials; 155 participants: RR: 0.97, 95% CI 0.90 to 1.05);
- the number of participants who die within 100 days (two trials, 95 participants: RR: 0.25, 95% CI 0.02 to 2.69. *low-quality evidence*);
- the number of participants who experienced any bleeding (two studies, 149 participants; RR:0.93, 95% CI 0.73 to 1.18, *low-quality evidence*), or clinically significant bleeding (two studies, 149 participants, RR: 1.03, 95% CI 0.75 to 1.43, *low-quality evidence*);
- the length of hospital stay (restrictive median 35.5 days (IQR: 31.2 to 43.8); liberal 36 days (IQR: 29.2 to 44)).

We are very uncertain whether the restrictive RBC transfusion strategy reduces:

- the risk of developing any serious infection (one study, 89 participants, RR: 1.23, 95% CI 0.74 to 2.04, very *low-quality evidence*).
- quality of life (one trial, 89 participants, fatigue score: restrictive median 4.8 (interquartile range (IQR) 4 to 5.2); liberal median 4.5 (IQR 3.6 to 5)).

Summary of main results from included NRS

We are very uncertain whether the restrictive RBC transfusion strategy decreases:

- the risk of death within 100 days (one study, 84 participants, restrictive 1 death; liberal 1 death);
- the risk of clinically significant bleeding (one study, 84 participants, restrictive 3; liberal 8;*very low-quality evidence*);
- the number of RBC transfusions (adjusted for age, sex and acute myeloid leukaemia type geometric mean 1.25; 95% CI 1.07 to 1.47 - data analysis performed by the study authors).

No NRS were found that looked at: quality of life; number of participants with any bleeding; serious infection; or length of hospital stay.

No studies were found that looked at: adverse transfusion reactions; arterial or venous thromboembolic events; length of intensive care admission; or readmission to hospital.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of a restrictive RBC transfusion strategy compared to a liberal RBC transfusion strategy for people diagnosed with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without a haematopoietic stem cell transplant (HSCT).

There was *low-quality evidence* that a restrictive RBC transfusion strategy has little or no effect on all-cause mortality, any bleeding or clinically significant bleeding. These were the only meta-analyses performed within this review

The results of these meta-analyses should not be interpreted without considering the impact of the following factors.

- The majority of participants in this review were adults with acute leukaemia treated with chemotherapy, the findings of this review may not be generalisable to children; people with other blood cancers; or people treated with a HSCT.
- Data on the review's primary outcome, all-cause mortality, was not provided by one trial (Webert 2008) (60 participants), therefore data were missing for over one third of participants within the included RCTs (155 participants).
- The recording of bleeding is subjective, and only one of the three studies that reported bleeding reported the method of assessing and grading bleeding (Webert 2008).
- There was little or no difference in all-cause mortality, this review's primary outcome, but the 95% confidence interval (0.25

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to 2.69) demonstrates that a clinically important difference in the proportion of participants who died could have been missed. If we assume a mortality rate of 3% within 100 days (data from De Zern 2016). We would need 1492 participants to have a 80% chance of detecting, as significant at the 5% level, an increase in all-cause mortality from 3% to 6%. The ongoing studies are planning to recruit 530 participants and therefore we may not be able to answer this review's primary outcome even when the ongoing studies have been completed.

- The early termination of one trial after recruiting only six participants influenced the availability of results (Robitaille 2013).
- Different restrictive triggers were tested in the RCTs; less than 70 g/L in both Robitaille 2013 and De Zern 2016, and less than 80 g/L in Webert 2008.
- Different restrictive triggers were tested in the RCTs; less than 120 g/L in both Webert 2008 and Robitaille 2013, and a much lower Hb transfusion threshold 80 g/L in De Zern 2016.
- The evidence of the safety of restrictive transfusion strategies among people with existing cardiovascular disease were also lacking as this subset of participants was excluded from the three of the included studies. Less stable participants were considered for inclusion in De Zern 2016 only.

Other important considerations in this review are:

- not all endpoints from all the studies could be incorporated into a meta-analysis due to differences in the ways the studies had reported the outcomes;
- some review outcomes were not reported by any of the included studies, for example, none of the studies reported transfusion reactions.

Quality of the evidence

There was evidence from three RCTs and one NRS.
The NRS only reported one outcome (number of RBC transfusions) that had been adjusted for confounding factors, and this analysis adjusted for only some of the potentially important confounding factors (age, sex and acute myeloid leukaemia type). The evidence from the NRS was very low according to GRADE criteria.
All of the RCTs were prone to bias. In all three RCTs participants and personnel were unblinded to the intervention, and in only one of the trials were outcome assessors blinded (Webert 2008). This is likely to reflect the inherent difficulties with blinding RBC transfusion trials because medical staff caring for participants cannot be blinded to their patients' blood results.
In De Zern 2016, some participants crossed over between the two transfusion strategies. Seven of 59 (11.9%; 95% CI, 4.91% to 22.93%) allocated to the restrictive transfusion strategy and two of 30 (6.7%; 95% CI, 0.82% to 22.07%) allocated to the liberal transfusion strategy crossed over during the study. Analysis was by intention-to-treat and therefore the ability to detect a difference between the two arms would have been reduced.
The ability to detect bias was limited by only two of the included studies having a trial registration or published protocol (De Zern 2016; Robitaille 2013).
We assessed the GRADE quality of evidence as low for:

- all cause mortality (RCT);
- bleeding episodes (RCT);
- length of hospital admission (RCT).

We downgraded the quality of evidence due to: the imprecision of the estimates (small number of included participants and there was a low number of events) and the indirectness of the evidence (most of the included participants were adults with acute leukaemia). We did not downgrade the evidence due to risk of bias due to lack of blinding because all-cause mortality is an objective outcome and the majority of the evidence for bleeding episodes was from a study in which outcome assessors were blinded (Webert 2008).
We assessed the GRADE quality of evidence as very low for:

- serious infection (RCT);
- quality of life (RCT);
- all-cause mortality (NRS);
- bleeding episodes (NRS).

For serious infection and quality of life, we downgraded the quality of evidence due to: the imprecision of the estimates, indirectness of the evidence (included participants were adults with acute leukaemia), and risk of bias (unblinded study).
For evidence from the NRS, we downgraded the quality of the evidence due to imprecision of the estimates.

Potential biases in the review process

There were no obvious biases within the review process. We conducted a wide search, which included ongoing trial databases and contact with researchers in the field; we carefully assessed the relevance of each paper identified; and we made no restrictions for the language in which the paper was originally published or its publication status. We performed all screening and data extractions in duplicate.We prespecified all outcomes and subgroups prior to analysis. The numbers of included studies were insufficient for us to combine to complete a funnel plot in order to examine the risk of publication bias.
None of the review authors were involved in the included or excluded studies.

Agreements and disagreements with other studies or reviews

Several reviews support the implementation of a more restrictive RBC transfusion strategies in a range of clinical settings. This has been shown in another Cochrane systematic review with a meta-

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analysis of 31 randomised controlled trials, involving 12,587 participants from mainly surgical and intensive-care settings (Carson 2016). The authors stated that the restrictive transfusion strategies were as safe as the liberal strategies for all-cause mortality, myocardial infarction, stroke, and thromboembolism. This review agreed with the findings from Carson 2016 regarding all-cause mortality, but we could not comment on myocardial infarction, stroke, and thromboembolism because none of our included studies reported these outcomes. The Carson 2016 review did not include some of this review's secondary outcomes. These outcomes were bleeding (not due to surgical procedures) and quality of life, both of which are relevant to people with haematological disorders. Carson 2016 did not perform a subgroup analysis for people with cardiac disease.

Several reviews have shown that a restrictive transfusion strategy decreases the number or RBC units transfused and number of participants being transfused (Carson 2016; Holst 2015). Carson 2016 and Holst 2015 had similar inclusion criteria, and both excluded trials in neonates. Holst 2015 (31 trials, 9813 participants) included data on six trials not included in Carson 2016 (two trials in infants and children undergoing cardiac surgery (Cholette 2011; De Gast-Bakker 2013), one trial in orthotopic liver transplantation reported as an abstract (Wu 2011), and three trials excluded from Carson 2016 for various reasons (Fortune 1987; Robertson 2014; Zygun 2009)). Carson 2016 included data from six trials not included in Holst 2015 (five more recent trials (De Zern 2016; Fan 2014; Jairath 2015; Murphy 2015; Nielsen 2014), and one older trial (Fisher 1956)). Our review agreed that a restrictive transfusion strategy reduced the number of transfusions a patient receives, but did not find a difference in the number of participants who received a RBC transfusion. This may be because the majority of trials in these other reviews are in people receiving surgery or who are in intensive care rather than people who have an underlying haematological disorder.

Docherty 2016 assessed the risk of a restrictive transfusion policy in people undergoing non-cardiac surgery who have cardiovascular disease (11 trials, 3033 participants). The results show that it may not be safe to use a restrictive transfusion threshold of less than 80 g/L in patients with ongoing acute coronary syndrome or chronic cardiovascular disease, although some of the results were uncertain. In this review we were unable to comment about people with cardiovascular disease due to lack of data.

Rohde 2014 focused on the risk of healthcare-associated infection such as pneumonia, wound infection, and sepsis (17 trials, 7593 participants). None of these trials were in people with haematological disorders. Rohde 2014 showed that a restrictive RBC transfusion strategy was associated with a significant reduction in the incidence of serious infection in hospital-admitted participants. Rohde 2014's finding agreed with Salpeter 2014 (three trials, 2364 participants), but disagreed with Carson 2016, which showed no difference in the risk of infection. The reviews differed, Rohde 2014 included unpublished data from four studies and data from neonatal studies; Salpeter 2014 only included published data for trials that used a restrictive threshold of 70 g/L in people in critical care or bleeding, and Carson 2016 included data from seven recently published trials not included in Rohde 2014 or Salpeter 2014. In this review, due to the lack of data we were very uncertain whether there was any difference in the risk of infection.

A possible association between the liberal transfusion strategy and a high incidence of developing veno-occlusive disease (VOD) was highlighted in Robitaille 2013, the study was stopped after enrolment of only six children because of this concern. In contrast, results from another RCT, on critically ill children reported no differences in the survival or adverse events between the two strategies (Lacroix 2007). However, the trigger for blood transfusion in the liberal group was below 95 g/L in comparison to 120 g/L for the liberal group in Robitaille 2013. Increased blood viscosity due to a high RBC level is one of the mechanisms known to increase the risk of VOD (Beck 1998).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to suggest that a restrictive red blood cell (RBC) transfusion strategy is superior to a liberal strategy in managing anaemia in people with haematological malignancies. Although restrictive blood transfusion strategies could potentially reduce blood use and lead to less exposure to blood products in this population.

The safest haemoglobin threshold for this population is still uncertain.

Implications for research

The low-quality evidence in this review is mainly based on adults with acute leukaemia who are having chemotherapy. The two ongoing studies (530 participants) are due to be completed by January 2018 and will provide additional information for adults with haematological malignancies. Adverse events related to transfusion should be reported in future studies. Further randomised controlled trials (RCTs) are required in children.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

De Zern 2016

Methods	**Type of Study:** Open-labelled single-centre parallel-arm randomised controlled trial **Type of publication**: Full **Setting and country**: USA **Number of centres**: single **Recruitment dates (start and end)**: April 15, 2014 to July 23 2015 **Median follow-up duration**: 5.9 weeks restrictive 6.1 weeks liberal **Was a power calculation performed?**
Participants	**Inclusion criteria:** acute leukaemia patients (AML, ALL, APL, high grade MDS) admitted with plans for inpatient myelosuppressive chemotherapy (with standard of care or protocol regimens) **Exclusion criteria:** • aged less than 18 years • acute coronary syndrome as defined by active chest pain, dynamic ECG changes, troponin greater than 2.5 • active blood loss • receiving erythropoietin stimulating agents prior to admission • chronic renal failure on renal replacement therapy • documented wish against transfusion for personal or religious beliefs **Number screened:** 162 eligible, only 112 approached due to resource limitations, 22 declined to participate **Number recruited:** 90 (1 participant withdrew prior to any transfusion) **Age:** restrictive: median 56 years (IQR 45.5 to 67): liberal: median 62.5 years (IQR 55.2 to 67.8) **Gender:** Male 49 (restrictive 33; liberal 16); Female 40 (restrictive 26; liberal 14) **Ethnicity:** not reported **Diagnosis:** AML (excluding APL) 73 (restrictive 50; liberal 23); APL 2 (restrictive 2; liberal 0); ALL 7 (restrictive 7; liberal 7) **Stage of disease:** not reported **Baseline haemoglobin level:** restrictive: median 83 g/L (IQR 75 to 89), liberal: median 89 g/L (IQR 81 to 92) **Treatment:** all received induction chemotherapy **Number analysed for primary outcome**: 89 participants (59 restrictive transfusion policy and 30 liberal transfusion policy) **Were participants with active bleeding explicitly excluded?** Yes **Were participants with a history of myocardial ischaemia/infarction explicitly excluded?** No, only participants with acute coronary syndrome where excluded
Interventions	**Restrictive RBC transfusion group**: participants will receive blood transfusion with transfusion threshold of 70 g/L Hb **Liberal RBC transfusion group:** participants will receive blood transfusion with threshold of 80 g/L Hb **Off-protocol transfusions:** There were two protocol deviations, one per arm, where patients were transfused before reaching their preset trigger accidentally

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De Zern 2016 (*Continued*)

	Red cell component: Standard leucocyte-reduced and irradiate red-cell units irradiated and prepared in additive solutions **Duration of red cell storage:** Not reported.
Outcomes	**Primary Outcome:** Safety of a restrictive transfusion threshold of 70 g/L compared to a standard transfusion threshold of 80 g/L at 60 days **Seondary Outcomes:** • Transfusion requirements (the number of red cells and platelets transfused per participant at 60 days) • The number of participants with neutropenic infections at 60 days • Grade 3 and 4 bleeding at 60 days • The length of hospital stay • Treatrment-related mortality at 60 days • End organ dysfunction at 60 days • Number of participants with Easten Cooperative Oncology Group (ECOG) performance status < 2 at 60 days • The incidence of treatment cross-over due to symptomatic anaemia at 60 days • Cost saving with a transfusion threshold reduction.
Assessment of Bleeding	Bleeding was graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 "The patients were assessed for bleeding and fatigue daily by the treating providers and documented in the daily progress notes. This was prospectively planned at the start of the trial and is the standard protocol for these patients at our institution. The bedside nurses as well as the physicians are required to document bleeding and fatigue daily. There were no adjudicators."
Quality of Life Assessment	Fatigue was assessed by the National Cancer Institue Fatigue Scale (Mendoza 1999). It is a rapid assessment of the fatigue severity in people with cancer. It is a numeric 10-point scale, with a score of 0 indicating no fatigue, a score of 5 interpreting as moderate fatigue and the maximum score of 10 is an indicate of the worst possible fatigue.This numeric scale was reported by the participants in the trial and the scoring form was completed by the clinical staff
Notes	**Trial Register ID:** National Institute of Health, Clinicaltrials.gov registry NCT02086773 **Supported by:** Sidney Kimmel Comprehensive Cancer Center **Conflicts-of-interest statement:** No conflict of interest was disclosed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random-number sequence was generated using computer software (JMP Version 9.0, SAS Institute). Treatment assignment was done with a 2:1 ratio, for the LOW:HIGH Hb trigger

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		groups, respectively. Blocking was used to specify a 2:1 ratio of treatment groups for each group of 18 consecutive patients."
Allocation concealment (selection bias)	Low risk	"Sealed opaque sequentially numbered envelopes were opened upon determination of inclusion for each patient in the trial. The randomization sequence and creation and numbering of the envelopes was performed by an investigator who did not enroll or consent patients for the trial."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...the study, by its nature, was not blinded and both the patients and their providers were aware of the treatment assignment groups." "There was initial inherent bias among nurses and physicians who were concerned about withholding transfusions from patients who need them, which may have increased the incidence of crossovers from the LOW to the HIGH group."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Lack of blinding could theoretically have influenced some outcome measures. For example, the fatigue scores may have been falsely low in the LOW group, resulting in an overestimation of fatigue difference between groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"One patient randomized to the LOW arm was not treated on study as the patient withdrew consent before any transfusions performed.All 89 patients randomly assigned and treated on the study protocol were included in the analysis. The patients who were approached and declined cited reasons for refusal as lack of willingness to participate in a clinical trial (seven patients), refusal for randomization (12 patients), and expressed concern of withholding of standard of care transfusion threshold (three patients)." "Both patient and clinician decisions to withdraw from study were slightly higher in the LOW arm: patient decision two of 59 (3.4%; 95% CI, 0.41%-11.71%) versus zero of 30 (0%; 95% CI, NA-11.57%)

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		, and clinician decision five of 59 (8.5%; 95% CI, 2.81%-18.68%) versus one of 30 (3.3%; 95% CI, 0.08%-17.22%). The two patient reasons for withdrawal of consent were both noted as decreased performance status or fatigue that they believed would improve after transfusion to a higher Hb. Upon subsequent query, both patients believed that they did feel better off the trial. The clinician withdrawals of consent were an inpatient fall attributed to anemia resulting in a head laceration (one patient), sepsis and goal of improved perfusion with higher Hb (two patients), inability to follow trial trigger due to extensive alloantibodies and the requirement to transfusion only when blood was available (one patient) , and a decreased patient performance status or fatigue perceived by the provider as related to anemia (one patient)."
Selective reporting (reporting bias)	Unclear risk	Planned outcomes reported in the trial registration but not reported in the published paper were: • Treatment-related mortality [Time Frame: 60 days] • End organ dysfunction [Time Frame: 60 days] • Number of patients with Eastern Cooperative Oncology Group (ECOG) performance status <2 [Time Frame: 60 days] • The incidence of treatment crossover due to symptomatic anaemia [Time Frame: 60 days] • Cost savings of the transfusion with a reduced transfusion threshold [Time Frame: 60 days] We contacted the study authors who said that these outcomes would be the basis of a second publication
Other bias	Unclear risk	"Baseline Hb levels were somewhat lower in the LOW threshold group, a median of 8.3 g/dL compared to 8.9 g/dL in the HIGH group (Wilcoxon p = 0.03)." "When the mean number of RBC units transfused was compared between arms of the study, adjusting for baseline Hb, the

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De Zern 2016 (*Continued*)

		LOW arm was transfused 8.0 (95% CI, 6. 9-9.1) units per patient while the HIGH arm patients received 11.7 (95% CI, 10. 1-13.2) units for an estimated difference (LOW minus HIGH) of 23.7 (95% CI, 25.6 to 21.7) units per patient, analysis of covariance p = 0.0003." "The incidence of crossover was also similar in the two study arms: seven of 59 (11.9%; 95% CI, 4.91%-22.93%) in the LOW arm and two of 30 (6.7%; 95% CI, 0.82%-22. 07%) in the HIGH (chi-square, p = 0.44) ." "The primary objective was the feasibility of conducting a larger randomized trial, which was defined a priori as achieving the following four criteria: 1) more than 50% of the eligible patients consented, 2) more than 75% of the patients randomized to the 7 g/dL arm tolerated the transfusion trigger, 3) fewer than 15% of patients crossed over from the lower transfusion threshold arm to the higher transfusion threshold arm, and 4) no indications for the need to pause the study for safety concerns. " All these criteria were met but the upper limit of the 95% CI was higher than the prespecified 15% limit for cross-over of participants

Jansen 2004

Methods	**Type of study**: Non-randomised controlled study (data collected prospectively for another study (HOVON 29), study designed retrospectively) **Type of publication**: Full **Setting and country**: Rotterdam, the Netherlands, Europe **Number of centres**: Two inpatient haematology units within a university hospital in Rotterdam (Erasmus Medical Centre & Daniel den Hoed Kliniek) **Recruitment dates (start and end)**: June 1, 1997 to December 7, 2001 **Mean follow-up duration**: Approximately one month (mean follow-up duration 30 days for restrictive, 32 days for liberal group) **Was a power calculation performed?** Not reported
Participants	**Inclusion criteria:** participants with newly diagnosed acute myeloid leukaemia (AML) treated with combination chemotherapy (ARA-C then Idarubicin) during first cycle of induction chemotherapy. Aged 15 to 60 years **Exclusion criteria:** A concurrent active malignancy, except stage I cervical carcinoma or basal cell carcinoma

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	Previous treatment with chemotherapy. Leukaemia following from a documented myelodysplasia with a duration of more than 6 months. Blastic crisis of chronic myeloid leukaemia or leukaemia developing from myeloproliferative diseases. Renal or liver function abnormalities. HIV positive serology. Severe cardiac, pulmonary or neurological disease (Information from HOVON 29 protocol). **Number screened:** unknown **Number recruited:** 84 (all included in analysis) **Age:** mean 42.8 years (SD 11.0) **Gender:** Male 39 (restrictive 18; liberal 21); Female 45 (restrictive 20; liberal 25) **Ethnicity:** not reported **Diagnosis:** acute myeloid leukaemia. (FAB Classification) M0 = 4 (restrictive 2; liberal 2); M1 = 22 (restrictive 11; liberal 11); M2 = 20 (restrictive 9; liberal 11); M3 = 8 (restrictive 3; liberal 5); M4 = 13 (restrictive 9; liberal 4); M5 = 15 (restrictive 2; liberal 13); M6 = 1 (restrictive 1; liberal 0) **Stage of disease:** all newly diagnosed. Risk category of disease according to HOVON leukaemia protocol: good risk (N = 13 (restrictive 7; liberal 6)); intermediate risk (N = 47 (restrictive 19; liberal 28)); poor risk (N = 21 (restrictive 11; liberal 10)); unknown (N = 3 (restrictive 1; liberal 2)) **Baseline haemoglobin level:** not reported **Treatment:** all received induction chemotherapy [ARA-C 200mg/m^2 (days 0 to 6) and Idarubicin 12mg/m^2 (days 0 to 3)] **Number analysed for primary outcome**: 84 participants (38 restrictive transfusion policy and 46 liberal transfusion policy) **Were participants with active bleeding explicitly excluded?** No **Were participants with a history of myocardial ischaemia/infarction explicitly excluded?** Yes, participants with severe cardiac disease where excluded
Interventions	Participants were assigned to one of the following transfusion strategies (based on where they were treated for their acute leukaemia): **i) Restrictive Policy** (Erasmus Medical Centre): If aged < 25 years red cell transfusion when Hb < 72 g/L; 25 to 50 years red cell transfusion when Hb < 80 g/L; aged 50 to 70, red cell transfusion when Hb < 88 g/L. Transfused one RBC unit at a time **ii) Liberal Policy** (Daniel den Hoed Kliniek): 2 units of RBCs given per transfusion when Hb < 96 g/L (transfusions given above threshold if signs/symptoms of decreased oxygen transportation capacity) **Off-protocol transfusions:** Not reported. Mean pre transfusion Hb 75 g/L (n = 3) for patients < 25 years when the restrictive strategy was to transfuse below 72 g/L **Red cell component:** leucocyte-reduced red-cell concentrates with a leucocyte count of less than 11x10^6/L, suspended in a 110 mL SAG-M solution, with a haematocrit of 0. 60 to a total volume of 265 mL **Duration of red cell storage:** not reported.
Outcomes	**Primary**: The number of RBC transfusions and the number of units given per transfusion **Secondary**: Clinical outcomes planned to be reported in the methods section included: mortality, bleeding, infections, cardiac dysrhythmias, cardiac dysfunction (WHO CTC grade 2 or higher), response to chemotherapy and myeloid:erythroid (M:E) ratio of the bone marrow smears. Additional transfusion outcomes reported include the number of platelet transfusions received, mean number of platelet adult therapeutic doses per transfusion; mean interval between RBC and platelet transfusions. (These transfusion

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Jansen 2004 (*Continued*)

	outcomes were not listed in the methods section) **Potential confounding variables taken into account:** sex, age and AML type
Assessment of Bleeding	Not reported
Quality of Life Assessment	Not assessed
Notes	**Trial registration:** No **Source(s) of funding**: Pharmaceutical, including Amgen, CKTO, Johnson & Johnson, Roche Nederland BV,Novartis Pharma B.V, as part of the HOVON 29 study. Funding of this study not reported **Conflicts-of-interest statement:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	A prospective cohort study not randomised. (Please see Table 3)
Allocation concealment (selection bias)	Low risk	This an observational cohort "cluster" study. As such there was no concealment of intervention, intervention depended on the site at which the participant was treated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not randomised. This an observational "cluster" study.There was no information if the status of each site was known to the participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcomes assessed were blind to the participants' allocation status
Incomplete outcome data (attrition bias) All outcomes	High risk	It is difficult to ascertain in this case, where all potential cases were accounted for in this study. The number of participants was not reported for all outcomes in the paper
Selective reporting (reporting bias)	High risk	Other pertinent end-points were not reported e.g. incidence of infection, infection agents post transplant complications
Other bias	Low risk	Multiple regression analysis was used and adjusted for potential confounding factors such as sex, age and AML type

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Robitaille 2013

Methods	**Type of study**: Planned as a multicentre randomised clinical trial **Type of publication**: Full **Setting and country**: Canada, North American **Number of centres**: Planned for six, only one centre recruited prior to trial closure by the Data Safety Monitoring Board **Recruitment dates (start and end)**: study start date: June 2009; planned study completion date: June 2015. Study stopped in August 2010 due to safety concerns **Mean follow-up duration**: Randomised on Day 0 with follow-up to Day +100 post-stem cell transplantation. Planned long-term events to be recorded at 1, 2, and 5 years of follow-up **Was a power calculation performed?** Yes. The trial originally planned to recruit 62 participants
Participants	**Inclusion criteria:** children aged 1 to 18 years who were undergoing an allogeneic BMT for a malignant or benign disease (except sickle cell disease) **Exclusion criteria:** children receiving autologous bone marrow transplant, cord blood transplant or peripheral stem cell transplant, sickle cell disease (since higher Hb level increases blood viscosity and puts these patients at risk for stroke); haematopoietic growth factor (G-CSF, GM-CSF, stem cell factor, erythropoietin) planned before transplantation (post-transplant decision of haematopoietic growth factors administration as required by the patient's condition were accepted); presence of an allo-antibody directed against RBC antigens **Number screened:** unknown (all consecutive BMT patients) **Number recruited:** six were randomised prior to early stopping (all included in analyses) **Age:** mean 11.7 years (range 5.9 to 15.9 years) **Gender:** male 2 (restrictive 1; liberal 1); female 4 (restrictive 2; liberal 2) **Ethnicity:** not reported **Stage of disease:** not reported **Diagnosis:** AML 3 (restrictive 1; liberal 2); MDS 2 (restrictive 1; liberal 1); immune deficiency 1 (restrictive 1) **Treatment:** myeloablative (busulfan-cyclophosphamide) allogeneic BMT; HLA-matched sibling 4 (restrictive 1; liberal 3); HLA-matched unrelated 1 (restrictive 1); HLA-mismatched related 1 (restrictive 1). GvHD prophylaxis: methotrexate and cyclosporin 4 (restrictive 1; liberal 3); methotrexate, cyclosporin & ATG 2 (restrictive 2) **Baseline haemoglobin level:** not reported **Number analysed for primary outcome**: N = 6 (3in restrictive group and 3 in liberal group) **Were participants with active bleeding explicitly excluded?** No **Were participants with a history of myocardial ischaemia/infarction explicitly excluded?** No
Interventions	Patients were randomised to one of the following transfusion strategies: **i) Restrictive**: Maintain Hb > 70 g/L. Transfused 10 to 15 mL/kg unless the clinical condition dictated otherwise **ii) Liberal**: Maintain Hb > 120 g/L. Transfused 10 to 15 mL/kg unless the clinical condition dictated otherwise **Off-protocol transfusions:** None received. 3 non-compliant days in the liberal group recorded due to lack of transfusion during a 24 hr period where Hb < 120 g/L **Red cell component:** leucocyte-reduced red-cell concentrates. **Duration of red cell storage:** mean length of storage was not significantly different

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	between study groups (restrictive 24.6 days; liberal 26.6 days)
Outcomes	**Primary**: Time to neutrophil recovery (defined as the time from transplantation to the first of 3 consecutive days with a neutrophil count $\geq$ 0.5 x 10^9/L) **Secondary**: 1) Time to platelet recovery (from transplant to the first of three consecutive days with platelets count $\geq$ 20 x 10^9/L, without need for platelet transfusions in last 7 days), 2) number of RBC and platelet transfusions, 3) length of hospitalisation, 4) immune reconstitution, 5) overall survival, 6) transplantation-related mortality, 7) relapse, 8) acute and chronic GvHD, and 9) chimerism. Long-term events and follow-up at 1, 2 and 5 years was part of the study plan
Assessment of Bleeding	Not reported
Quality of Life Assessment	Not assessed
Notes	**Trial registration:** NCT00937053; Canadian Blood and Marrow Transplant Group CBMTG 0603 **Source(s) of funding**: Fonds de la Recherche en Sante (grant 9967 and 24460) and C17 research network (public) **Conflicts-of-interest statement:** the authors declared no conflict of interest. **Stopping of trial:** The study was stopped after recruiting only 6 participants because of safety concerns. All 3 participants in the liberal transfusion arm developed VOD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Web-based randomisation sytem " Randomization of patients was done on the first day of their conditioning regimen using a web-based randomization system"
Allocation concealment (selection bias)	Low risk	Web-based randomisation sytem " Randomization of patients was done on the first day of their conditioning regimen using a web-based randomization system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study, no blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Study not complete, as it was stopped early by the study's DSMB after recruiting 6 participants. All participants in the liberal transfusion arm were withdrawn from the

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Robitaille 2013 (*Continued*)

		study prior to day 100. "A patient found the RBC transfusions bothering and withdrew from the trial for this reason on day +10. Another patient was withdrawn at day +25 by the treating physician because of the occurrence of VOD as well as 2 episodes of minor allergic reactions to the transfusion. The last patient was withdrawn on day +8 when VOD occurred." All participants in the restrictive arm continued on the planned transfusion policy until day 100. All participants recruited were followed up until day 100
Selective reporting (reporting bias)	High risk	Study not complete, as it was stopped early by the study's DSMB. The statistical analysis for the study's primary outcome was not performed. Secondary outcomes not reported were: time to platelet recovery; length of hospitalisation; immune reconstitution; relapse; and chimerism
Other bias	High risk	The early stopping of the trial could substantially overestimate the results with only six participants enrolled

Webert 2008

Methods	**Type of study**: A multicentre, single-blinded pilot randomised-controlled trial **Type of publication**: Full paper **Setting and country**: Canada, North America **Number of centres**: 4 tertiary haematology centres **Recruitment dates (start and end)**: 01/03/2003 to 31/10/2004 [20 months] **Mean follow-up duration**: 25.9 days (SD 8.4) in the restrictive group, 23.6 days (10.0 SD) in the liberal group. 1482 days of observation. The study observation periods started on the day after randomisation and ended when one of the following criteria was met: Participant's platelet count was greater than 20 x 10^9/L for 7 days without a platelet transfusion or when it was not possible to perform daily bleeding assessments or when participant's physician requested removal from the study or when death occurred **Was a power calculation performed?**: No
Participants	**Inclusion criteria:** adults (age >16 years) with acute leukaemia admitted for induction or re-induction chemotherapy or adult patients admitted to receive conditioning for HLA antigen-matched myeloablative allogeneic SCT for a haematologic malignancy **Exclusion criteria:** acute promyelocytic leukaemia (French-American British M3); aplastic anaemia; history of myocardial infarction or angina in the past 6 months; refusal to receive blood transfusions; history of inherited or acquired coagulation disorders; known haemolytic disease; international normalized ratio (INR) of greater than 1.5 (uncorrected by the administration of vitamin K); evidence of significant acute bleeding during the

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	first 12 hours after admission to the hospital (defined as evidence of ongoing blood loss accompanied by a decrease in the Hb concentration of at least 30 g/L during the first 12 hours after admission or a requirement of at least 3 units of RBCs during the same period); presence of an alloantibody that could limit compatible blood supply; previous enrolment in this trial; and unwillingness or inability to give informed consent **Number screened:** 84 (9 ineligible; 15 declined to participate) **Number recruited:** 60 (all included in analyses) **Age:** mean 47.9 years (range 18 to 77 years) **Gender:** Male 32 (restrictive 18; liberal 14); Female 28 (restrictive 11; liberal 17) **Ethnicity:** not reported **Diagnosis:** AML 39 (restrictive 19; liberal 20); ALL 5 (restrictive 3; liberal 2); haematological malignancy (unspecified) 16 (restrictive 7; liberal 9) **Stage of disease:** newly diagnosed AML 30 (restrictive 15; liberal 15); relapsed AML 9 (restrictive 4; liberal 5); unknown 21 (restrictive 10; liberal 11) **Treatment:** chemotherapy 44 (restrictive 22; liberal 22); SCT 16 (restrictive 7; liberal 9) **Baseline haemoglobin level:** restrictive: 96.3 g/L, liberal: 96.5 g/L **Number analysed for across outcomes**: For bleeding 60 (29 restrictive and 31 liberal) , for platelets and RBC and Hb levels 57(29/28) **Were participants with active bleeding explicitly excluded?** Yes. Participants with acute bleeding during the first 12 hours after admission were excluded **Were participants with a history of myocardial ischaemia/infarction explicitly excluded?** Yes, participants with a history of myocardial infarction or angina in the last 6 months
Interventions	Patients were randomised to one of the following transfusion strategies: **i) Restrictive**: two units of RBC transfused when Hb below 80 g/L **ii) Liberal**: two units of RBC transfused when Hb below 120 g/L **Off-protocol transfusions:** 36.4% of transfusions received in restrictive group when Hb > 80g/L; 29.8% of transfusions received when Hb > 120g/L in the liberal group **Red cell component:** leucocyte-reduced before storage by Canadian blood services. volume 240 mL to 340 mL per unit, suspended in AS-3, estimated haematocrit of 0.55 to 0.65 **Duration of storage:** not reported
Outcomes	**Primary and secondary**: All five outcomes reported in the study considered relevant to the study feasibility and no single primary outcome was selected The outcomes of the study included; 1) bleeding (the occurrence graded by the WHO score, the time to the first bleed and number of bleeding days); 2) proportion of days of thrombocytopenia where the Hb level was within the targeted range; 3) blood product utilisation (number of RBC and platelet units) and blood donor exposure; 4) the ability to document bleeding symptoms and bleeding severity; and 5) participant number enrolled
Assessment of Bleeding	Clinical assessment of bleeding was performed each morning and reported according to the WHO scale. Each morning Monday to Friday a trained blinded assessor performed the observation. Saturday and Sunday assessments were performed retrospectively by reviewing the participant's chart All bleeding episodes were independently reviewed by an adjudication committee who were blinded to the participants' treatment assignments and Hb levels

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	Bleeding categorised by the committee by severity: no bleeding, non-clinically significant bleeding, and clinical significant bleeding
Quality of Life Assessment	Not assessed
Notes	**Trial registration: Unknown.** **Source(s) of funding**: Canadian Blood Services & CIHR Canada Research Chair (Public source) Conflicts-of-interest statement: Unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated "A computer-generated random treatment allocation schedule was developed with a variable blocking factor with the size of the blocks selected in a random fashion from a limited number of possibilities"
Allocation concealment (selection bias)	Low risk	Computer generated "patients were randomly assigned with an Internet-based randomisation web site"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants and clinicians were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded, a member of the study group would assess clinical records to check if any bleeding episodes were missed. Bleeding reviews at weekend performed on Monday through review of patient's chart (not all bleeding episodes may have been recorded). Other reported outcomes are "hard" and/or "utilisation" outcomes, which could be argued to less influenced by un-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up until study completion.
Selective reporting (reporting bias)	Low risk	No missing data identified. The analysis is assumed be intention-to-treat but neither explicitly confirmed in the report

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Webert 2008 (*Continued*)

Other bias	Unclear risk	Number of study days after target Hb levels reached differed were variable between groups (467 days restrictive; 410 days liberal), as it took longer for liberal group to reach the Hb threshold. Due to the way that bleeding assessed some bleeding episodes might had been missed

ALL = acute lymphocytic leukaemia
AML = acute myeloid leukaemia
APL = acute promyelocytic leukaemia
CML: Chronic myelogenous leukaemia
BMT = bone marrow transplant
DSMB = Data Safety Monitoring Board
G-CSF = granulocyte-colony stimulating factor
GM-CSF = Granulocyte-macrophage colony-stimulating factor
GvHD = graft versus host disease
Hb = haemoglobin
IQR = interquartile range
MDS = myelodysplastic syndrome
RBC(s) = red blood cell(s)
SCT = stem cell transplant
SD = standard deviation
VOD = veno-occlusive disease

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

Study	Reason for exclusion
Abels 1991	Participants: Oncology participants Intervention: transfusion rates studied not different triggers
Almeida 2013	Participants: non-haematological oncological participants included. An RCT involving adults with cancer who were undergoing abdominal surgery
Bercovitz 2011	Study design: review
Berger 2012	Study design: Ambidirectional cohort study Intervention: one versus two units studied as opposed to a haemoglobin trigger
Bruun 2011	Participants: non-haematological oncological participants included
Carson 2014	A review including RCTs conducting on people with myocardial infarction, brain injury, stroke, or haematological disorders

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(*Continued*)

Holst 2013	Review
ISRCTN26088319	An RCT involving people with myelodysplastic syndrome.
Lightdale 2012	Study design: cohort study using retrospective control.
Mear 2014	Study design: cohort study using historical control.
NCT00202371	Study withdrawn prior to enrolment
NTR2684	Participants: participants receiving chemotherapy were excluded
Paananen 2009	Study design: no prospective element.
Patil 2013	Study design: no prospective element.
Prescott 2016	Review.
Yakymenko 2015	Participants: non-haematological oncological participants included. An RCT involving adults with cancer

RCT = randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT02099669

Methods	Red Blood Cell Transfusion Thresholds and QOL in MDS (EnhanceRBC): a Pilot, Feasibility Study Open-label, parallel, randomised controlled trial
Participants	**Inclusion Criteria:** • All patients with MDS ≥18 years of age • Transfusion dependent: at least 1 transfusion per month in the last 8 weeks • Hb < 100 g/L pre transfusion • Life expectancy > 6 months **Exclusion Criteria:** • Unstable cardiac disease (Canadian Cardiovascular Society (CCS) III/IV angina or New York Heart Association (NYHA) III/IV congestive heart failure) requiring the transfusion target range to remain > 85 g/L to 100 g/L at all times • ECOG ≥3 • Patients with red cell antibodies against high frequency antigens or multiple antibodies (would potentially delay finding blood) • Patients on ESA's or disease modifying agents (like azacitidine) for their MDS
Interventions	• Experimental: Liberal transfusion strategy- maintain Hb level between 110 g/L and 120 g/L: to achieve this, 2 units of pRBCs are transfused when Hb level is < 105 g/L and 1 unit of RBCs when Hb level is 105 g/L to 110 g/L.

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NCT02099669 (*Continued*)

	Intervention: Other: RBC transfusions • Active Comparator: Restrictive transfusion strategy- maintain Hb level between 85 g/L and 100 g/L: to achieve this, 2 units of pRBCs will be transfused when the Hb level is < 80 g/L and 1 unit of pRBCs when Hb level is 80 g/L to 85 g/L • Intervention: Other: RBC transfusions
Outcomes	**Primary Outcome** Percentage compliance of fortnightly HB The percentage compliance of fortnightly Hb being within or above the target range of the RBC transfusion threshold assigned (after the 4 week run-in at study start as defined above). We will consider this study feasible and worthy of future development into a larger randomised trial (powered for QOL difference) if compliance is ≥70%. A compliance rate of 50% to 70%, would not exclude going forward with such an RCT but only after careful discussion and statistical planning **Secondary Outcomes** • Measures of feasibility. Number of participants 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 comparing the 2 RBC transfusion thresholds above. • Adverse eventsThe rate of transfusion reactions (as defined by TTISS (Transfusion Transmitted Injuries Surveillance System by Public Health Agency of Canada)). Rate of adverse events such as cardiac events and thromboembolic events as per NCI CTCAE version 4.0 criteria • Alloimmunisation rates • Haemosiderosis • The impact on transfusion-associated haemosiderosis rates and burdens (as measured by changes in ferritin levels and iron chelating medications) • Overall utilisation of blood • Time commitment • The overall time commitment per group, measured as the time spent in transfusion medicine clinic
Notes	**Planned recruitment:** 30 adults **Sponsor:** Sunnybrook Health Sciences Centre **Trial registration:** NCT02099669 on 26 March 2014 **Location of trial:** Canada **Number of study centres:** 1

ECOG = Eastern Cooperative Oncology Group
ESA(s) = erythropoiesis-stimulating agent(s)
Hb = haemoglobin
MDS = myelodysplastic syndrome
pRBC(s) = packed red blood cell(s)
QOL = quality of life
RBC(s) = red blood cell(s)
RCT = randomised controlled trial

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

Chantepie 2015

Trial name or title	Randomized trial of two transfusion strategies in patients hospitalized for acute leukemia induction chemotherapy or hematopoietic stem cells with medico-economic evaluation (1 VERSUS 2 CGR)
Methods	Open-labelled single-centre parallel-arm randomised controlled trial
Participants	**Inclusion criteria** 18 years or older with either acute leukaemia diagnosis receiving intensive chemotherapy or autologous transplantation for lymphoma, allogeneic stem cell transplantation **Exclusion criteria** • acute promyelocytic leukaemia • known ischaemic heart disease • acute or chronic respiratory disease • history of ischaemic stroke • disseminated intravascular coagulation • haemorrhagic syndrome • HSCT conditioning not usually associated with pRBC transfusion need such as: ○ auto-HSCTconditioned with alkeran (myeloma patients) ○ non-myelo-ablative allo-HSCT conditioned using only fludarabine and total body irradiation (TBI) 2 gray • erythropoietin treatment • autoimmune haemolytic anaemia • pregnancy • renal impairment with an estimated (modified diet in renal disease; MDRD) creatinine clearance < 50 mL/min) • chronic liver disease or day-1 (AST/ALT) ≥ 2.5 upper limit of normal (ULN) (except if related to leukaemia) • total bilirubin ≥ 1.5 ULN • cirrhosis • age < 18 years • any organ failure
Interventions	**Two packed red blood cells Transfusion group (liberal):** Two RBC packs will be transfused to the study participants with anaemia defined as a Hb level below 80 g/L. Clinical and biological monitoring will be carried out later each day. If the Hb is < 80 g/L, two new pRBCs are transfused and so on **Single red blood packed cells Transfusion group (restrictive):** Single RBC pack will be administered in patient with anaemia defined as a Hb level below 80 g/L. Clinical and biological monitoring will be carried out later each day. If the Hb is < 80 g /L, a single unit is transfused and so on
Outcomes	**Primary outcome measure:** • Number of severe complications (grade 3 or more) up to 1 month after the last day of hospitalisation , (This includes: stroke, transient ischaemic attack, acute coronary syndrome, heart failure, arrhythmias or conduction cardiac disease, deep vein thrombosis, pulmonary embolism, elevated troponin, transfer to intensive care unit, death from any cause, new or progressive radiographic infiltrates, infections related to transfusion) **Secondary outcome measures:** All will be assessed up to 1 month after the last day of hospitalisation, these will include:

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Chantepie 2015 (*Continued*)

	• number of RBC components transfused • incidence of bleeding (number of participants with bleeding grade 3 or more) • the number of patients with each complication defined in the primary endpoint • transfusion-related events (any complication declared by the physician to be related to the transfusion • number of days with Hb > 80 g/L • time to erythroid recovery • quality of life duration of neutropenia (from first day with neutrophils < 0.5 x 10^9/L to first day with neutrophils > 0.5 x 10^9/L) • transfusion performance (difference between Hb level before and 24 hours after transfusion) • number of RBC units transfused after leaving the unit, failure to respect the randomisation arm (number of participants who received 2 RBC units instead of single RBC unit).
Starting date	**Study Start Date:** January 2016 **Estimated Study Completion Date:** January 2018 **Estimated Primary Completion Date:** January 2018 (Final data collection date for primary outcome measure)
Contact information	DR Sylvain P Chantepie, University Hospital, Caen, France chantepie-s@chu-caen.fr
Notes	**Planned recruitment:** 230 adults **Sponsor:** University Hospital, Caen **Trial registration:** NCT02461264 on 3 June 2015 **Location of trial:** Caen, France **Number of study centres:** 1

Tay 2011

Trial name or title	Transfusion of red cells in hematopoietic stem cell transplantation (TRIST)
Methods	Open-labelled multicentre parallel-arm randomised controlled trial
Participants	**Inclusion Criteria:** • People aged 16 to 70 undergoing either an autologous or allogeneic HSCT for any haematological malignancy **Exclusion Criteria:** • Pregnant or lactating at the time of enrolment • Already received red cell transfusion after HSCT but prior to enrolment • Unable/unwilling to provide informed consent • People receiving HSCT for any non-malignant indication
Interventions	**Liberal Strategy (Red cell transfusion trigger of 90 g/L):** Participants will receive 2 units of packed RBCs if the Hb level is < 90 g/L, based the day's CBC to target a Hb level of 90 to 110 g/L **Restrictive Red cell Transfusion Strategy (Red cell transfusion trigger of 70 g/L):** Participants will receive 2 units of pRBCs if the Hb level is < 70 g/L, based on the day's CBC to target a Hb level of 70 g/L to 90 g/L

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Tay 2011 (*Continued*)

Outcomes	**Primary Outcome:** Quality of Life by FACT-BMT **Secondary Outcomes:** 1) Transfusion requirements (red cells, platelets and plasma), 2) Transplant-related mortality, 3) Maximum grade of GvDH, 4) Veno-occlusive disease, 5) Serious infections, 6) Bearman Toxicity Score, 7) Bleeding, 8) Quality of life by EQ 5D, FACT-Anemia, 9) Number of Hospitalisations, 10) Number of ICU admissions
Starting date	March 2011
Contact information	Dr Jason Tay, The Ottawa Hospital Blood and Marrow Programme, The Ottawa Hospital, Ottawa, Canada. jtay@ottawahospital.on.ca
Notes	**Planned recruitment:** 300 adults **Estimated study completion date**: June 2016 **Trial Register ID:** National Institute of Health, Clinicaltrials.gov registry NCT01237639 **Supported by:** Canadian Blood Services (R&D Intramural Grants Competition 2010) and Canadian Institute of Health Research **Location of trial:** Canada **Number of study centres:** multiple

ALT = alanine transaminase
AST = aspartate transaminase
GvHD = graft versus host disease
HSCT = haematopoietic stem cell transplant
ICU = intensive care unit
pRBC(s) = packed red blood cell(s)
RBC(s) = red blood cell(s)

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DATA AND ANALYSES

Comparison 1. Restrictive versus liberal red blood cell transfusion RCTs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality-at 31 to 100 days	2	95	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.02, 2.69]
2 Mortality due to chemotherapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Number of participants with any bleeding	2	149	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.18]
4 Number of participants with clinically significant bleeding	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.75, 1.43]
5 Severe or life-threatening bleeding events	2	149	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.39, 6.30]
6 Number of participants with serious infection episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Number of participants with VOD	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
8 Number of participants with RBC transfusion from study entry	3	155	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.05]
9 Number of participants with RBC Transfusion after reaching Hb >80 g/L for restrictive & Hb > 120 g/L for liberal	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Mean number of RBC (units) transfusions per participant during the entire study period	2	95	Mean Difference (IV, Fixed, 95% CI)	-3.58 [-5.66, -1.49]
11 Number of participants with PLT transfusions from the study entry	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

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Analysis 1.1. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 1 All-cause mortality-at 31 to 100 days.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 1 All-cause mortality-at 31 to 100 days

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	1/59	2/30		100.0 %	0.25 [0.02, 2.69]
Robitaille 2013	0/3	0/3			Not estimable
Total (95% CI)	**62**	**33**		**100.0 %**	**0.25 [0.02, 2.69]**

Total events: 1 (Restrictive), 2 (Liberal)
Heterogeneity: not applicable
Test for overall effect: Z = 1.14 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 2 Mortality due to chemotherapy.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 2 Mortality due to chemotherapy

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	1/59	1/30		0.51 [0.03, 7.85]



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Analysis 1.3. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 3 Number of participants with any bleeding.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 3 Number of participants with any bleeding

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	19/59	11/30		35.0 %	0.88 [0.48, 1.60]
Webert 2008	25/29	28/31		65.0 %	0.95 [0.79, 1.15]
Total (95% CI)	**88**	**61**		**100.0 %**	**0.93 [0.73, 1.18]**

Total events: 44 (Restrictive), 39 (Liberal)

Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 0.62 (P = 0.54)

Test for subgroup differences: Not applicable



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Analysis 1.4. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 4 Number of participants with clinically significant bleeding.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 4 Number of participants with clinically significant bleeding

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	9/59	5/30		23.8 %	0.92 [0.34, 2.49]
Webert 2008	22/29	22/31		76.2 %	1.07 [0.79, 1.45]
Total (95% CI)	**88**	**61**		**100.0 %**	**1.03 [0.75, 1.43]**

Total events: 31 (Restrictive), 27 (Liberal)

Heterogeneity: $Chi^2 = 0.11$, df = 1 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable



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Analysis 1.5. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 5 Severe or life-threatening bleeding events.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 5 Severe or life-threatening bleeding events

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	5/59	2/30		84.6 %	1.27 [0.26, 6.17]
Webert 2008	1/29	0/31		15.4 %	3.20 [0.14, 75.55]
Total (95% CI)	**88**	**61**		**100.0 %**	**1.57 [0.39, 6.30]**
Total events: 6 (Restrictive), 2 (Liberal)					
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.53)					
Test for subgroup differences: Not applicable					



Analysis 1.6. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 6 Number of participants with serious infection episodes.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 6 Number of participants with serious infection episodes

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
De Zern 2016	29/59	12/30		1.23 [0.74, 2.04]



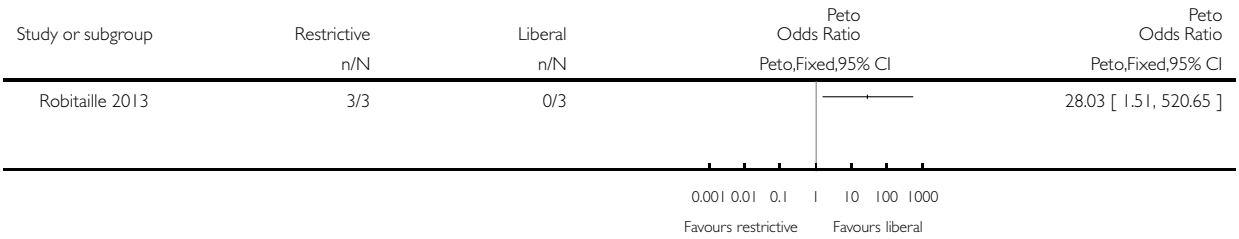
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Analysis 1.7. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 7 Number of participants with VOD.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 7 Number of participants with VOD

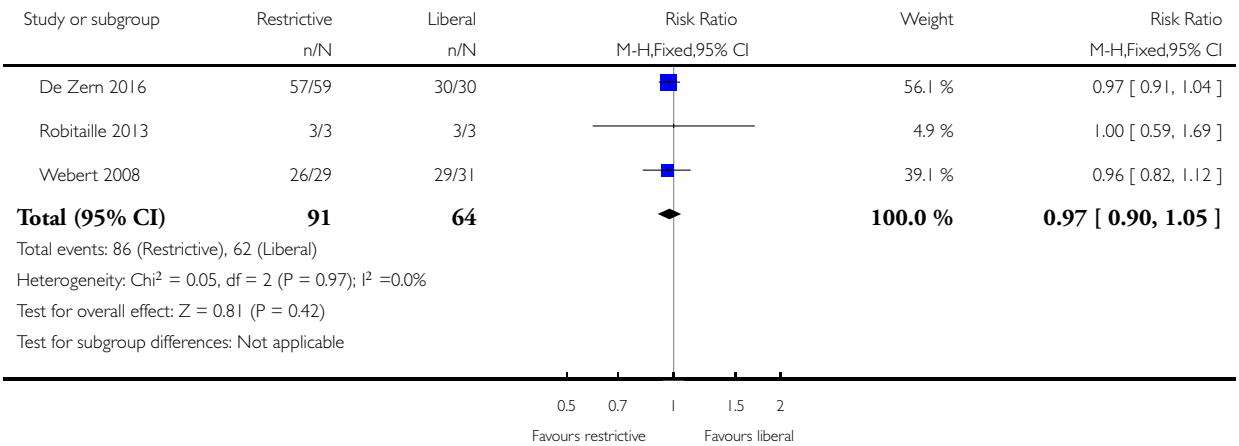


Analysis 1.8. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 8 Number of participants with RBC transfusion from study entry.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 8 Number of participants with RBC transfusion from study entry



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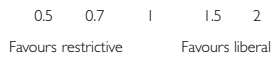
Analysis 1.9. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 9 Number of participants with RBC Transfusion after reaching Hb >80 g/L for restrictive & Hb > 120 g/L for liberal.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 9 Number of participants with RBC Transfusion after reaching Hb >80 g/L for restrictive % Hb > 120 g/L for liberal

Study or subgroup	Restrictive n/N	Liberal n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Webert 2008	24/29	28/28		0.83 [0.70, 0.99]



Analysis 1.10. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 10 Mean number of RBC (units) transfusions per participant during the entire study period.

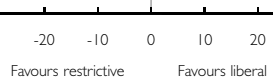
Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 10 Mean number of RBC (units) transfusions per participant during the entire study period

Study or subgroup	Restrictive N	Mean(SD)	Liberal N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Robitaille 2013	3	1.3 (0.58)	3	8.7 (5.5)		11.1 %	-7.40 [-13.66, -1.14]
De Zern 2016	59	8.2 (4.2)	30	11.3 (5.4)		88.9 %	-3.10 [-5.31, -0.89]
Total (95% CI)	**62**		**33**			**100.0 %**	**-3.58 [-5.66, -1.49]**

Heterogeneity: Chi^2 = 1.61, df = 1 (P = 0.20); I^2 =38%
Test for overall effect: Z = 3.36 (P = 0.00077)
Test for subgroup differences: Not applicable



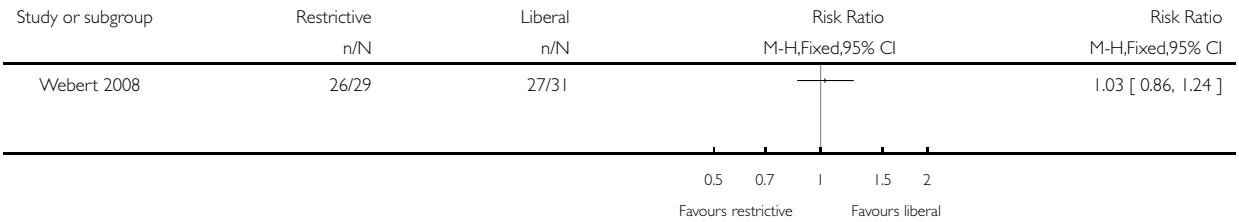
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Analysis 1.11. Comparison 1 Restrictive versus liberal red blood cell transfusion RCTs, Outcome 11 Number of participants with PLT transfusions from the study entry.

Review: Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Comparison: 1 Restrictive versus liberal red blood cell transfusion RCTs

Outcome: 11 Number of participants with PLT transfusions from the study entry



ADDITIONAL TABLES

Table 1. Important complications of transfusion and their approximate frequency in the UK extrapolated from data from the Serious Hazards of Transfusion (SHOT) scheme 2014 (Bolton-Maggs 2014) compared with low income countries (WHO 2015)

Transfusion Risk	Frequency in the UK (units transfused) (Bolton-Maggs 2014)	Frequency in low income countries (WHO 2015)
ABO incompatible red cell transfusion	3.7 in 1 million (10 cases per 2663488 transfusions)	unknown
Transfusion-related acute lung injury	0.4 in 1 million (10 cases per 2663488 transfusions)	unknown
Transfusion associated circulatory overload	34.1 in 1 million (91 cases per 2663488 transfusions)	unknown

Table 2. Frequency of infection in donated blood in high and low income countries (WHO 2015)

Transfusion transmitted infection	**Frequency in high income countries**	**Frequency in low income countries**
HIV	2 in 100,000 (IQR 0.4 in 100,000 to 20 in 100,000)	850 in 100,000 (IQR 480 in 100,000 to 2000 in 100,000)
HBV	20 in 100,000 (IQR 8 in 100,000 to 24 in 100,000)	3590 in 100,000 (IQR 2010 in 100,000 to 6080 in 100,000)

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Table 2. Frequency of infection in donated blood in high and low income countries (WHO 2015) (*Continued*)

HCV	20 in 100,000 (IQR 0.4 in 100,000 to 22 in 100,000)	1070 in 100,000 (IQR 630 in 100,000 to 1690 in 100,000)

IQR=interquartile range

Table 3. Jansen 2004: 'Risk of bias' assessment for observational studies using the Newcastle-Ottawa Scale (Wells 2013)

Risk of Bias	Assessment	Support for judgement
Selection (one star each, maximum four stars)	**2 stars**	
Representativeness of the exposed cohort	0 stars	This study only included participants with AML as opposed to all patients with haematological malignancies
Selection of the non-exposed cohort	0 star	Participants in the control were from a second haematology centre, but there was no information to reassure that this cohort was drawn from the same community as exposed cohort
Ascertainment of exposure	1 star	Secondary analyses from HOVON 29, prospective randomised controlled trial
Demonstration that outcome of interest was not present at start of study	1 stars	The primary outcome and other outcomes were defined and were based on events that occurred after the study started
Comparability of cohort on design and analyses (maximum of two stars) Recognition of at least 75% of the main potential confounding factors (2 stars) Recognition of 50% to 75% of the main potential confounding factors (1 star)	**0 stars**	< 50% of potential cofounders considered and sex, age and AML type were adjusted for in the multiple regression model. There was no discussion on previous severe bleeding, use of anticoagulation, use of radiotherapy in addition to chemotherapy, previous cardiovascular disease, previous alloimmunisation or performance status
Outcome (one star each, maximum of four stars)	**2 stars**	
Assessment of outcome	0 stars	Not described
Was follow-up long enough for outcomes to occur?	1 star	Yes, 31 days from chemotherapy
Adequacy of follow-up of cohorts	0 star	Reported for all, except unclear for infection, mean Hb during follow-up, total number of platelet/red blood cell units received
Follow-up equal between groups for primary and secondary outcomes?	1 star	Follow-up not significantly different
Additional concerns		None

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Table 3. Jansen 2004: 'Risk of bias' assessment for observational studies using the Newcastle-Ottawa Scale (Wells 2013) (*Continued*)

Overall assessment	**4 stars**	

AML = acute myeloid leukaemia
Hb = haemoglobin

Table 4. Review secondary outcome-red blood cell transfusion

Study	No. of participants received RBC transfusion during the study period	Mean no. RBC units transfusions/participant during study period	Number of participant-days with RBC transfusions	Proportion of participant-days with RBC transfusions	Mean Hb within first +100 days:	Number of RBC units per transfusion	Interval between RBC transfusions (mean) (days)
RCTs							
De Zern 2016	**Restrictive:** 57/59 **Liberal:** 30/30	**Restrictive:** mean 8.2 (SD 4.2) **Liberal:** mean 11.3 (SD 5.4)	NR	NR	**Restrictive:** mean 33.6 (SD 1.4) **Liberal:** mean 33.2 (SD 2.0)	NR	NR
Robitaille 2013	**Restrictive:** 3/3 **Liberal:** 3/3	**Restrictive:** (mean 1.3 [SD 0.58]; median 1 [range 1 to 2; SE 0.33]) **Liberal:** (mean 8.7 [SD 5.5]; median 9 [range 3 to 14; SE 3.2])	NR	NR	**Restrictive:** [mean pre transfusion Hb 69 g/L (range 69 g/L to 70 g/L) no SD] **Liberal:** [mean pre transfusion Hb 106 g/L (range 118 g/L to 132 g/L) no SD]	NR	NR
Webert 2008	**Restrictive:** 26/29 (24/29 from when Hb ≥80 g/L) **Liberal:** 29/31 (28/	NR	**Restrictive:** 75 (70/467 days of observation once reached target Hb) **Liberal:** 113 g/L (72/	**Restrictive:** 0.151 (0.150 after study Hb threshold reached) **Liberal:** 0.233 (0.176 after study Hb	NR	NR	NR

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Table 4. Review secondary outcome-red blood cell transfusion (*Continued*)

	28 from when Hb ≥ 120g/L)		410 days of observation once reached target Hb)	threshold reached) [RR 1. 56; 95% CI 1. 16 to 2.10] [RR 1.18: 95% CI 0.90 to 1.54; once study Hb threshold reached][a]			
NRS							
Jansen 2004	NR	**Restrictive:** mean 9.6 (SD 3.9); Median 9 (SE 0.6); Range 3 to 21 **Liberal:** mean 10.8 (SD 2.9); Median 11.0 (SE 0.4); Range 6 to 21	NR	NR	**Restrictive:** Age < 25 Hb 7.5 (n = 3); 25-50 yrs Hb 8.0 (n = 22) ; Age 50-70 years Hb 8.3 (n = 13) **Liberal:** Age < 25 years Hb 8.8 (n = 3) ; 25-50 years Hb 9. 3 (n = 32); 50-70 years Hb 9. 5 (n = 11)	**Restrictive:** Mean 1.3 (SD 0.5); Median 1.0 (SE 0.03); range 1-4 **Liberal:** Mean 1.82 (SD 0.4); Median 2 (SE 0. 03); Range 1-5	**Restrictive:** 3. 1 days (No SD) **Liberal:** 3 days (No SD)

CI = confidence interval
Hb = haemoglobin
RBC = red blood cell
RR - risk ratio
SD = standard deviation
SE = standard error
Trial HB: Restrictive ≥ 80g/L and Liberal ≥ 120g/L
[a] Data analysed by study authors, reported as relative risks derived from adjusted Cox regression models, allowing for repeated measures.

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Table 5. Review secondary outcomes - platelet and red cell transfusions

Study ID	Number of PLTs transfused per participant	Number of participant-days with PLT transfusions	Proportion of participant-days with RBC transfusions	Interval between PLT transfusions (mean & SD)(days)	Number of PLT units per transfusion (mean & SD) (units)	Nmber of PLT transfusion per participant
RCTs						
De Zern 2016	NR	NR	NR	NR	NR	**Restrictive:** median:9 (IQR: 5.5 to 12.5) **Liberal;** median: 9 (IQR: 7 to 12)
Robitaille 2013	NR	NR	NR	NR	NR	NR
Webert 2008	**Restrictive:** 26/29 from study entry, 26 from when target Hb reached **Liberal:** 27/31 from study entry; 26 from when target Hb reached	**Restrictive:** 124 from study entry; 122 from Hb 80 g/L to 100 g/L **Liberal:** 0.265 from study entry; 0.283 from when Hb > 120 g/L	**Restrictive:** 0.249 from study entry; 0.261 from when Hb 8-10 **Liberal:** 0.265 from study entry; 0.283 from when Hb > 12 [RR 1.06; 95% CI 0.74 to 1.52] [RR 1.02: 95% CI 0.73 to 1.44; once study Hb threshold reached][a]	NR	NR	NR
NRS						
Jansen 2004	**Restrictive**: Mean 7.5 (SD 3.8); median 7 (SE 0.6); range 2 to 18 **Liberal:** Mean 8.5 (SD 4.9); median 7 (SE 0.7); range 2 to 30 P > 0.05	NR	NR	**Restrictive:** 4 days (No SD) **Liberal:** 3.8 days (No SD)	**Restrictive:** Mean 1.1 (SD 0.4); median 1 (SE 0.03); range 1 to 4 **Liberal**: Mean 1.2 (SD 0.5); Median 1 (SE 0.03); range 1 to 4	NR

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[a] Data analysed by study authors, reported as relative risks derived from Cox regression models.
IQR = Interquartile range

APPENDICES

Appendix 1. CENTRAL search strategy on the 15 June 2016

#1 MeSH descriptor: [Blood Transfusion] this term only
#2 MeSH descriptor: [Blood Component Transfusion] explode all trees
#3 MeSH descriptor: [Erythrocyte Transfusion] this term only
#4 (erythrocyte* or "red cell*" or blood or RBC*) near/5 (transfus* or unit*)
#5 (("red cell*" or RBC* or erythrocyte* or "red blood cell*" or "whole blood" or transfus*) near/5 (trigger* or level* or threshold* or rule* or target* or restrict* or liberal* or reduc* or limit*))
#6 (("red cell*" or blood) near/3 (management or sparing or support or strateg*))
#7 ("allogeneic blood" or (unit* near/2 blood) or "allogenic blood" or (blood near/2 exposure) or "donor blood" or "blood product" or "blood products" or "blood component" or "blood components" or "blood support")
#8 (h*emotransfus* or hypertransfus* or h*emotherap*)
#9 ("red cell*" or "red blood cell*" or RBC* or transfus*):ti
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Hematologic Neoplasms] explode all trees
#12 MeSH descriptor: [Hematologic Diseases] this term only
#13 MeSH descriptor: [Leukemia] explode all trees
#14 MeSH descriptor: [Lymphoma] explode all trees
#15 MeSH descriptor: [Neoplasms, Plasma Cell] explode all trees
#16 MeSH descriptor: [Anemia, Aplastic] explode all trees
#17 MeSH descriptor: [Bone Marrow Diseases] explode all trees
#18 MeSH descriptor: [Thrombocytopenia] explode all trees
#19 (thrombocytop*eni* or leuk*emi* or lymphom* or "aplastic an*emi*" or "refractory an*emi*" or myelodysplas* or myeloproliferat* or myelom* or plasmacytom*)
#20 (lymphogranulomato* or histiocy* or granulom* or thrombocyth*emi* or polycyth*emi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulos* or reticulosarcom* or MDS or RAEB or "RAEB-t")
#21 (burkitt* next (lymph* or tumo*r)) or lymphosarcom* or brill-symmer* or sezary
#22 ((h*ematolog* or blood or "red cell*" or "white cell*" or lymph* or marrow or platelet*) near/3 (malignan* or oncolog* or cancer* or neoplasm* or carcinoma*))
#23 MeSH descriptor: [Antineoplastic Agents] explode all trees
#24 MeSH descriptor: [Remission Induction] explode all trees
#25 MeSH descriptor: [Antineoplastic Protocols] explode all trees
#26 MeSH descriptor: [Stem Cell Transplantation] explode all trees
#27 MeSH descriptor: [Bone Marrow Transplantation] this term only
#28 MeSH descriptor: [Radiotherapy] explode all trees
#29 MeSH descriptor: [Lymphatic Irradiation] this term only
#30 (("bone marrow" or "stem cell*" or "progenitor cell*") near/2 (transplant* or graft* or engraft* or rescu*))
#31 ((h*ematolog* or h*emato-oncolog*) near/2 patients)
#32 (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT)
#33 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 ((consolidat* or induct* or maintenance or conditioning*) near/3 (therap* or treat* or regimen* or patient*))

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#35 ((therap* or induc*) near/3 remission*)
#36 ((cytosta* or cytotox*) near/2 (therap* or treat* or regimen*))
#37 ((multimodal* or multi-modal*) near/3 (treat* or therap*))
#38 (combi* near/2 modalit*)
#39 MeSH descriptor: [Transplantation Conditioning] explode all trees
#40 mini-tra?splant*
#41 MeSH descriptor: [Transplantation, Homologous] explode all trees
#42 (allograft* or allo-graft* or allotransplant* or allo-transplant* or ((allogen* or allo-gen*) near/5 (transplant* or trasplant* or graft* or rescue*)) or homograft* or homo-graft* or homotransplant* or homo-transplant* or homotrasplant* or homo-trasplant*)
#43 MeSH descriptor: [Transplantation, Autologous] this term only
#44 (autograft* or auto-graft* or autotransplant* or auto-transplant* or autotra?splant* or auto-tra?splant* or (autolog* near/5 (transplant* or graft* or trasplant* or rescu*)))
#45 #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
#46 #33 or #45
#47 #10 and #46
#

Appendix 2. MEDLINE (Ovid) search strategy on the 15 June 2016

1. BLOOD TRANSFUSION/
2. *BLOOD COMPONENT TRANSFUSION/
3. ERYTHROCYTE TRANSFUSION/
4. ((erythrocyte* or red cell* or blood or RBC*) adj
5 (transfus* or unit*)).tw,kf. 5. ((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj3 (trigger* or level* or threshold* or rule* or target* or restrict* or liberal* or reduc* or limit*)).tw,kf.
6. (allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or bl ood component* or blood support).tw,kf.
7. (h?emotransfus* or hypertransfus* or h?emotherap*).tw,kf.
9. (red cell* or erythrocyte* or transfus* or whole blood or RBC*).ti.
10. BLOOD COMPONENT TRANSFUSION/ not (EXCHANGE TRANSFUSION, WHOLE BLOOD/ or PLASMA EXCHANGE/ or PLATELET TRANSFUSION/ or exp LEUKOCYTE TRANSFUSION/)
11. ERYTHROCYTES/ or (red cell* or red blood cell* or erythrocyte* or RBC*).ti.
12. 10 and 11
13. or/1-9,12
14. exp Hematologic Neoplasms/ or Hematologic Diseases/
15. exp Leukemia/ or exp Lymphoma/
16. exp Neoplasms, Plasma Cell/
17. exp Anemia, Aplastic/
18. exp Bone Marrow Diseases/
19. exp Thrombocytopenia/
20. (thrombocytopeni* or thrombocytopaeni* or leukemi* or leukaemi* or lymphom* or myelodysplas* or myeloproliferat* or myelom* or plasm??ytom*).tw,kf,ot.
21. (lymphogranulomato* or histiocy* or granulom* or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom* or MDS or RAEB or RAEB-t).tw,kf,ot.
22. ((aplastic or refractory) adj an?emi*).tw,kf,t.
23. ((burkitt* adj (lymph* or tumo?r)) or lymphosarcom* or brill-symmer* or sezary).tw,kf,ot.
24. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm* or carcinoma*)).tw,kf,ot.
25. exp Antineoplastic Agents/ or exp Remission Induction/ or exp Antineoplastic Protocols/
26. exp Stem Cell Transplantation/ or Bone Marrow Transplantation/ or exp Radiotherapy/
27. exp Lymphatic Irradiation/

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28. (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow adj2 (transplant* or graft* or engraft* or rescu*))).tw,kf,ot.
29. (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw,kf,ot.
30. ((h?ematolog* or h?ematooncolog* or h?emato-oncolog*) adj3 patients).tw,kf,ot.
31. (h?ematooncolog* or h?emato-oncolog*).ti.
32. or/14-3133. exp Remission Induction/ 34. exp Antineoplastic Protocols/
35. ((consolidat* or induct* or maintenance or conditioning*) adj6 (therap* or treat* or regimen* or patient*)).tw,kf,ot. 36. ((therap* or induc*) adj3 remission*).tw,kf,ot.
37. ((cytosta* or cytotox*) adj2 (therap* or treat* or regimen*)).tw,kf,ot.
38. ((multimodal* or multi-modal*) adj3 (treat* or therap*)).tw,kf,ot. 39. (combi* adj3 modalit*).tw,kf,ot.
40. or/33-39
41. Transplantation Conditioning/
42. mini-tra?splant*.tw.
43. exp Transplantation, Homologous/
44. (allograft* or allo-graft* or allotransplant* or allo-transplant* or ((allogen* or allo-gen*) adj5 (transplant* or trasplant* or graft* or rescue*)) or homograft* or homo-graft* or homolog* or homotransplant* or homo-transplant* or homotrasplant* or homo-trasplant*).tw,kf,ot.
45. Transplantation, Autologous/
46. (autograft* or auto-graft* or autotransplant* or auto-transplant* or autotra?splant* or auto-tra?splant* or (autolog* adj5 (transplant* or graft* or trasplant* or rescue*))).tw,kf,ot.
47. or/41-46
48. 32 or 40 or 47
49. 13 and 48
50. (201312* or 2014* or 2015*).dc,ed. or ("2013" or "2014" or "2015" or "2016").yr.
51. 49 and 5

Appendix 3. Embase (Ovid) search strategy on the 15 June 2016

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,kf.
5. ((red cell* or RBC* or erythrocyte* or red blood cell* or whole blood or transfus*) adj3 (trigger* or level* or threshold* or rule* or target* or restrict* or liberal* or reduc* or limit*)).tw,kf.
6. (allogeneic blood or (unit* adj2 blood) or allogenic blood or (blood adj2 exposure) or donor blood or blood product* or blood component* or blood support).tw,kf.
7. (h?emotransfus* or h?emotherap* or hypertransfus*).tw,kf.
8. (transfus* or red cell* or red blood cell* or RBC* or whole blood).ti.
9. or/1-8
10. Hematologic Malignancy/
11. Lymphoma/
12. NonHodgkin Lymphoma/
13. Hodgkin Disease/
14. exp Myeloproliferative Disorder/
15. exp Aplastic Anemia/
16. exp Thrombocytopenia/
17. (thrombocytopeni* or thrombocytopaeni* or leukemi* or leukaemi* or lymphom* or aplast* anemi* or aplast* anaemi* or myelodysplas* or myeloproliferat* or myelom* or plasm??ytom*).tw,kf,ot.
18. (lymphogranulomato* or histiocy* or granulom* or thrombocythemi* or thrombocythaemi* or polycythemi* or polycythaemi* or myelofibros* or AML or CLL or CML or Hodgkin* or nonhodgkin* or reticulosis or reticulosarcom* or MDS or RAEB or RAEB-t).tw,kf,ot.
19. ((burkitt* adj (lymph* or tumo?r)) or lymphosarcom* or brill-symmer* or sezary).tw,kf,ot.

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20. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj3 (malignan* or oncolog* or cancer* or neoplasm* or carcinoma*)).tw,kf,ot.
21. exp Stem Cell Transplantation/
22. exp Bone Marrow Transplantation/
23. exp Chemotherapy/
24. exp Radiotherapy/
25. exp Antineoplastic Agent/
26. exp Immunosuppressive Treatment/
27. Remission/
28. (chemotherap* or antineoplast* or anti-neoplast* or radiotherap* or radio-therap* or chemoradiotherap* or chemo-radiotherap* or stem cell* or progenitor cell* or (bone marrow adj2 (transplant* or graft* or engraft* or rescu*))).tw,kf,ot.
29. (ASCT or ABMT or PBPC or PBSCT or PSCT or BMT or SCT or HSCT).tw,kf,ot.
30. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*) adj2 patients).tw,kf,ot.
31. (malignan* or oncolog* or cancer*).ti.
32. ((consolidat* or induct* or maintenance or conditioning*) adj6 (therap* or treat* or regimen* or patient*)).tw,kf,ot.
33. ((therap* or induc*) adj3 remission*).tw,kf,ot.
34. ((cytosta* or cytotox*) adj2 (therap* or treat* or regimen*)).tw,kf,ot.
35. ((multimodal* or multi-modal*) adj3 (treat* or therap*)).tw,kf,ot.
36. (combi* adj3 modalit*).tw,kf,ot.
37. Allotransplantation/
38. Autotransplantation/
39. mini-tra?splant$.tw.
40. (allograft* or allo-graft* or allotransplant* or allo-transplant* or ((allogen* or allo-gen*) adj5 (transplant* or trasplant* or graft* or rescue*)) or homograft* or homo-graft* or homolog* or homotransplant* or homo-transplant* or homotrasplant* or homo-trasplant*).tw,kf,ot.
41. (autograft* or auto-graft* or autotransplant* or auto-transplant* or autotra?splant* or auto-tra?splant* or (autolog* adj5 (transplant* or graft* or trasplant* or rescue*))).tw,kf,ot.
42. or/10-41
43. 9 and 42
44. limit 43 to dd=20131201-20151105

Appendix 4. CINAHL (EBSCOhost) search strategy on the 15 June 2016

S1 (MH "Hematologic Neoplasms+")
S2 (MH "Leukemia+")
S3 (MH "Lymphoma+")
S4 (MH "Multiple Myeloma")
S5 TI (leukemi* or leukaemi* or lymphoma* or myeloma* or plasmacytoma or plasma cell dyscrasia or AML or CLL or CML or Hodgkin* or haematolymphoid* or hematolymphoid*) OR AB (leukemi* or leukaemi* or lymphoma* or myeloma* or plasma cell dyscrasia or AML or CLL or CML or Hodgkin* or haematolymphoid* or hematolymphoid*)
S6 TI ((haematoncolog* or hematoncolog* or haemato-oncolog* or hemato-oncolog*) N5 patient*) OR AB ((haematoncolog* or hematoncolog* or haemato-oncolog* or hemato-oncolog*) N5 patient*)
S7 (MH "Myelodysplastic Syndromes")
S8 myelodysplas* or "bone marrow dysplasia" or preleukemi* or preleukaemi* or dysmyelopoietic or dysmyelopoiesis
S9 refractory N2 (anemia or anaemia)
S10 MDS or RAEB or RAEB-t
S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
S12 (MH "Blood Transfusion")
S13 (MH "Blood Component Transfusion")
S14 (MH "Erythrocyte Transfusion")
S15 (erythrocyte* or red cell* or red blood cell* or RBC*) N5 (transfus* or unit*)

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S16 (transfus* or erythrocyte* or red cell* or red blood cell* or RBC*) N5 (trigger* or level* or target* or threshold* or rule* or restrict* or liberal*)
S17 red cell* management or red cell* sparing or red cell* support or red cell* strategy
S18 (red cell* N2 reduc*) or (red cell* N3 requirement*)
S19 hemotransfus* or haemotransfus* or hemotherap* or haemotherap*
S20 TI (red cell* or red blood cell* or erythrocyte* or RBC* or blood)
S21 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S22 S11 AND S21

Appendix 5. PubMed search strategy (epublications only) on the 15 June 2016

#1 (((erythrocyte*[TI] OR blood[TI]) AND (unit*[TI] AND trigger*[TI] OR level*[TI] OR threshold*[TI] OR rule*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR requir*[TI] OR reduc*[TI] OR limit*[TI])) OR (hemotransfus*[TI] OR haemotransfus*[TI] OR hemotherap*[TI] OR haemotherap*[TI] OR "red cell*"[TI] OR "red blood cell*"[TI] OR RBC*[TI] OR transfus*[TI]))
#2 ((random* OR blind* OR "control group" OR placebo* OR controlled OR cohort* OR nonrandom* OR observational OR retrospective* OR prospective* OR comparative OR comparator OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))
#3 (thrombocytopeni*[TI] OR thrombocytopaeni*[TI] OR leukemi*[TI] OR leukaemi*[TI] OR lymphom*[TI] OR "aplastic anemia"[TI] OR "aplastic anaemia"[TI] OR myelodysplas*[TI] OR myeloproliferat*[TI] OR myeloma[TI] OR lymphogranulomato*[TI] OR histiocy*[TI] OR granulom*[TI] OR thrombocythemi*[TI] OR thrombocythaemi*[TI] OR polycythemi*[TI] OR polycythaemi*[TI] OR myelofibros*[TI] OR AML[TI] OR CLL[TI] OR CML[TI] OR Hodgkin*[TI] OR burkitt*[TI] OR lymphosarcom*[TI] OR brill-symmer*[TI] OR sezary[TI] OR ((haematolog*[TI] OR hematolog*[TI] OR blood[TI] OR red cell*[TI] OR white cell*[TI] OR marrow[TI] OR platelet*[TI]) AND (malignan*[TI] OR oncolog*[TI] OR cancer*[TI] OR neoplasm*[TI] OR carcinoma*[TI])) OR chemotherap*[TI] OR radiotherap*[TI] OR chemoradiotherap*[TI] OR "stem cell"[TI] OR "stem cells" OR "progenitor cell"[TI] OR "progenitor cells"[TI] OR bone marrow transplant*[TI] OR bone marrow graft*[TI] OR "bone marrow rescue"[TI] OR rituximab[TI] OR antineoplast*[TI] OR anti-neoplast*[TI] OR ASCT[TI] OR ABMT[TI] OR PBPC[TI] OR PBSCT[TI] OR PSCT[TI] OR BMT[TI] OR SCT[TI] OR HSCT[TI] OR "haematology patients"[TI] OR "hematology patients"[TI] OR "haematological patients"[TI] OR "hematological patients"[TI] OR "hemato-oncology patients"[TI] OR "haemato-oncology patients"[TI] OR remission[TI] OR ((consolidat*[TI] OR induct*[TI] OR maintenance[TI] OR conditioning*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI] OR patient*[TI])) OR ((cytosta*[TI] OR cytotox*[TI]) AND (therap*[TI] OR treat*[TI] OR regimen*[TI])) OR ((multimodal*[TI] OR multi-modal*[TI]) AND (treat*[TI] OR therap*[TI])) OR (combi*[TI] AND modalit*[TI]) OR (allograft*[TI] OR allo-graft*[TI] OR allotransplant*[TI] OR allo-transplant*[TI] OR ((allogen*[TI] OR allo-gen*[TI]) AND (transplant*[TI] OR trasplant*[TI] OR graft*[TI] OR rescue*)) AND TI OR homograft*[TI] OR homo-graft*[TI] OR homolog*[TI] OR homotransplant*[TI] OR homo-transplant*[TI] OR homotrasplant*[TI] OR homo-trasplant*[TI]) OR (autograft*[TI] OR autograft*[TI] OR autotransplant*[TI] OR auto-transplant*[TI] OR mini-transplant*[TI]) OR (autolog*[TI] AND (transplant*[TI] OR graft*[TI] OR trasplant*[TI] OR rescu*[TI]))
#4 #1 AND #2 AND #3

Appendix 6. Transfusion Evidence Library on the 15 June 2016

Clinical Specialty: Haematology, Malignant
Subject Area: Red Cells

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Appendix 7. LILACS search strategy on the 15 June 2016

db:("LILACS") AND type˙of˙study:("cohort" OR "clinical˙trials" OR "case˙control" OR "systematic˙reviews") AND ((leukemi* OR leukaemi* OR lymphoma* OR myeloma* OR plasmacytoma OR plasma cell dyscrasia OR AML OR CLL OR CML OR Hodgkin* OR haematolymphoid* OR hematolymphoid* OR haematolog* OR hematolog* OR ((haematopoietic OR hematopoietic) AND (malignan* OR oncolog* OR cancer* OR neoplas*)) OR haematooncolog* OR hematooncolog* OR haemato-oncolog* OR hemato-oncolog* OR myelodysplas* OR bone marrow OR stem cell* OR preleukemi* OR preleukaemi* OR dysmyelopoietic OR dysmyelopoiesis OR refractory anemia OR refractory anaemia OR MDS OR RAEB*) AND (transfus* OR ((erythrocyte* OR red cell* OR red blood cell* OR RBC*) AND (unit* OR trigger* OR level* OR target* OR threshold* OR rule* OR restrict* OR liberal* OR requir* OR reduc* OR limit*)) OR hemotransfus* OR haemotransfus* OR hemotherap* OR haemotherap*))

Appendix 8. INDMED search strategy on the 15 June 2016

(leukemia OR leukaemia OR lymphoma OR myeloma OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR haematology OR hematology OR myelodysplasia OR marrow OR stem cell OR preleukemia OR preleukaemia OR dysmyelopoietic OR dysmyelopoiesis) AND (transfusion OR red cells OR red blood cells OR RBC OR RBCs OR hemotransfusion OR haemotransfusion OR hemotherapy OR haemotherapy OR hypertransfusion) AND (randomized OR randomised OR randomly OR blind OR blinded OR trial OR cohort OR observational OR control OR controlled OR groups)OR((haematopoietic OR hematopoietic OR haematological OR hematological) AND (malignancyOR oncology OR cancer OR neoplasm)) AND (transfusion OR red cells OR red blood cells OR RBC OR RBCs OR hemotransfusion OR haemotransfusion OR hemotherapy OR haemotherapy OR hypertransfusion) AND (randomized OR randomised OR randomly OR blind OR blinded OR trial OR cohort OR observational OR control OR controlled OR groups)

Appendix 9. KOREAMED search strategy on the 15 June 2016

Limits: ("Clinical Trial" [PT] OR "Comparative Study" [PT] OR "Evaluation Studies" [PT] OR "Meeting Abstract" [PT] OR "Meta-Analysis" [PT] OR "Multicenter Study" [PT] OR "Practice Guideline" [PT] OR "Randomized Controlled Trial" [PT] OR "Review" [PT]) AND "Blood Transfusion" [MH] OR transfus* [TI] OR "red cell*" [TI] OR "red blood cell*" [TI

Appendix 10. Web of Science (CPCI-S) search strategy on the 15 June 2016

#1 TI=(leukemi* OR leukaemi* OR lymphoma* OR myeloma* OR plasmacytoma OR "plasma cell dyscrasia" OR AML OR CLL OR CML OR Hodgkin* OR haematolymphoid* OR hematolymphoid* OR haematolog* OR hematolog* OR haematooncolog* OR hematooncolog* OR haemato-oncolog* OR hemato-oncolog* OR myelodysplas* OR "bone marrow" OR "stem cell" OR "stem cells" OR preleukemi* OR preleukaemi* OR dysmyelopoietic OR dysmyelopoiesis OR "refractory anemia" OR "refractory anaemia" OR MDS OR RAEB*) OR TS=(leukemi* OR leukaemi* OR lymphoma* OR myeloma* OR plasmacytoma OR "plasma cell dyscrasia" OR AML OR CLL OR CML OR Hodgkin* OR haematolymphoid* OR hematolymphoid* OR haematolog* OR hematolog* OR haematooncolog* OR hematooncolog* OR haemato-oncolog* OR hemato-oncolog* OR myelodysplas* OR "bone marrow" OR "stem cell" OR "stem cells" OR preleukemi* OR preleukaemi* OR dysmyelopoietic OR dysmyelopoiesis OR "refractory anemia" OR "refractory anaemia" OR MDS OR RAEB*)
#2 TI=((haematopoietic OR hematopoietic) AND (malignan* OR oncolog* OR cancer* OR neoplas*)) OR TS=((haematopoietic OR hematopoietic) AND (malignan* OR oncolog* OR cancer* OR neoplas*))
#3 #1 OR #2
#4 TI=(erythrocytes OR red cells OR red blood cells OR RBCs OR transfus* OR hemotransfus* OR haemotransfus* OR hemotherap* OR haemotherap*) OR TS=(erythrocytes OR red cells OR red blood cells OR RBCs OR transfus* OR hemotransfus* OR haemotransfus* OR hemotherap* OR haemotherap*)
#5 TI=(randomi* OR blind* OR trial OR cohort* OR observational* OR control* OR groups) OR TS=(randomi* OR blind* OR trial OR cohort* OR observational* OR control* OR groups)
#6 #3 AND #4 AND #5
)
#9 #7 AND #8

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Appendix 11. ClinicalTrials.gov search strategy on the 15 June 2016

Study Type: All
Conditions: blood cancers OR hematological OR nonhodgkin OR leukemia OR lymphoma OR myeloma OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR myelodysplasia OR preleukemia OR dysmyelopoietic OR dysmyelopoiesis OR "refractory anemia" OR aplastic
Interventions: "red cell transfusion" OR "blood transfusion" OR "red cells" OR RBCs OR "red blood cells"
OR Search Terms: stem cell transplantation OR stem cells OR bone marrow transplantation OR blood cancers OR hematological OR nonhodgkin OR leukemia OR lymphoma OR myeloma OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR myelodysplasia OR preleukemia OR dysmyelopoietic OR dysmyelopoiesis OR "refractory anemia" OR aplastic Study
Type: All Interventions: "red cell transfusion" OR "blood transfusion" OR "red cells" OR RBCs OR "red blood cells"

Appendix 12. ISRCTN search strategy on the 15 June 2016

("red cell transfusion" OR "blood transfusion" OR "red blood cell transfusion") AND (leukemia OR leukaemia OR lymphoma OR myeloma OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR haematology OR hematology OR myelodysplasia)

Appendix 13. WHO ICTRP search strategy on the 15 June 2016

Title OR interventions: transfusion OR red cells OR red blood cells OR RBCs
Conditions: blood cancers OR haematological OR nonhodgkin OR leukemia OR lymphoma OR myeloma OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR myelodysplasia OR preleukemia OR dysmyelopoietic OR dysmyelopoiesis OR refractory anemia OR aplastic anemia
Recruitment Status: ALL

Appendix 14. EUDRACT search strategy on the 15 June 2016

(transfusion OR red cell OR red blood cell) AND (leukemia OR lymphoma OR myeloma OR hematology OR haematology OR haematological OR haematological OR plasmacytoma OR Hodgkin OR haematolymphoid OR hematolymphoid OR myelodysplasia OR preleukemia OR dysmyelopoietic OR dysmyelopoiesis OR refractory anemia)

CONTRIBUTIONS OF AUTHORS

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

Reem Malouf: searching, selection of studies, eligibility and quality assessment, data extraction and analysis, and drafting.

Marialena Trivella: protocol development and statistical expert.

Dean Fergusson: a content and methodological expert for this review and contributed to the preparation of the protocol and the proposed analysis.

Sally Hopewell: protocol development and methodological expert.

Mike Murphy: protocol development and content expert

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DECLARATIONS OF INTEREST

Lise Estcourt is partly funded by NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. Award of this national government grant by NIHR does not lead to a conflict of interest.

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Dean A Fergusson: None known

Mike Murphy: None known.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Aspects listed in the review protocol (Butler 2014) that were not implemented due to lack of data.

Publication bias: We did not perform a formal assessment of potential publication bias (small-trial bias) because we included fewer than 10 trials within this review (Sterne 2011). With only a few studies were included this was not applicable.

Review outcome and reporting results: We performed meta-analyses when appropriate. However, due to the small number of studies included in this review and the heterogeneity across these studies this was not always possible. We therefore, summarised and discussed results.

Subgroup analyses: We could not perform any of the subgroup analyses that we initially planned, this was because of absence of data and ultimately we were only able to conduct one meta-analysis involving the three included randomised controlled trials (RCTs).

Meta-regression: This was not possible as this was advised with a subgroup that contained more than 10 studies (Deeks 2011)

Sensistivity analyses: This was not possible as we were only able to combine relevant data extracted from the three included studies in one meta-analysis.

Summary of findings: We listed the most important clinical outcomes for the comparison of the two transfusion methods in the review protocol. However, the hospital rate admission outcome was not reported in any of the included studies.

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