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Transfusion thresholds for guiding red blood cell transfusion (Review)

Carson JL, Stanworth SJ, Dennis JA, Trivella M, Roubinian N, Fergusson DA, Triulzi D, Dorée C, Hébert PC

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[Intervention Review]

Transfusion thresholds for guiding red blood cell transfusion

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ABSTRACT

Background

The optimal haemoglobin threshold for use of red blood cell (RBC) transfusions in anaemic patients remains an active field of research. Blood is a scarce resource, and in some countries, transfusions are less safe than in others because of inadequate testing for viral pathogens. If a liberal transfusion policy does not improve clinical outcomes, or if it is equivalent, then adopting a more restrictive approach could be recognised as the standard of care.

Objectives

The aim of this review update was to compare 30-day mortality and other clinical outcomes for participants randomised to restrictive versus liberal red blood cell (RBC) transfusion thresholds (triggers) for all clinical conditions. The restrictive transfusion threshold uses a lower haemoglobin concentration as a threshold for transfusion (most commonly, 7.0 g/dL to 8.0 g/dL), and the liberal transfusion threshold uses a higher haemoglobin concentration as a threshold for transfusion (most commonly, 9.0 g/dL to 10.0 g/dL).

Search methods

We identified trials through updated searches: CENTRAL (2020, Issue 11), MEDLINE (1946 to November 2020), Embase (1974 to November 2020), Transfusion Evidence Library (1950 to November 2020), Web of Science Conference Proceedings Citation Index (1990 to November 2020), and trial registries (November 2020). We checked the reference lists of other published reviews and relevant papers to identify additional trials. We were aware of one trial identified in earlier searching that was in the process of being published (in February 2021), and we were able to include it before this review was finalised.

Selection criteria

We included randomised trials of surgical or medical participants that recruited adults or children, or both. We excluded studies that focused on neonates.

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Eligible trials assigned intervention groups on the basis of different transfusion schedules or thresholds or 'triggers'. These thresholds would be defined by a haemoglobin (Hb) or haematocrit (Hct) concentration below which an RBC transfusion would be administered; the haemoglobin concentration remains the most commonly applied marker of the need for RBC transfusion in clinical practice. We included trials in which investigators had allocated participants to higher thresholds or more liberal transfusion strategies compared to more restrictive ones, which might include no transfusion. As in previous versions of this review, we did not exclude unregistered trials published after 2010 (as per the policy of the Cochrane Injuries Group, 2015), however, we did conduct analyses to consider the differential impact of results of trials for which prospective registration could not be confirmed.

Data collection and analysis

We identified trials for inclusion and extracted data using Cochrane methods. We pooled risk ratios of clinical outcomes across trials using a random-effects model. Two review authors independently extracted data and assessed risk of bias. We conducted predefined analyses by clinical subgroups. We defined participants randomly allocated to the lower transfusion threshold as being in the 'restrictive transfusion' group and those randomly allocated to the higher transfusion threshold as being in the 'liberal transfusion' group.

Main results

A total of 48 trials, involving data from 21,433 participants (at baseline), across a range of clinical contexts (e.g. orthopaedic, cardiac, or vascular surgery; critical care; acute blood loss (including gastrointestinal bleeding); acute coronary syndrome; cancer; leukaemia; haematological malignancies), met the eligibility criteria. The haemoglobin concentration used to define the restrictive transfusion group in most trials (36) was between 7.0 g/dL and 8.0 g/dL. Most trials included only adults; three trials focused on children.

The included studies were generally at low risk of bias for key domains including allocation concealment and incomplete outcome data.

Restrictive transfusion strategies reduced the risk of receiving at least one RBC transfusion by 41% across a broad range of clinical contexts (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.53 to 0.66; 42 studies, 20,057 participants; high-quality evidence), with a large amount of heterogeneity between trials (I^2 = 96%).

Overall, restrictive transfusion strategies did not increase or decrease the risk of 30-day mortality compared with liberal transfusion strategies (RR 0.99, 95% CI 0.86 to 1.15; 31 studies, 16,729 participants; I^2 = 30%; moderate-quality evidence) or any of the other outcomes assessed (i.e. cardiac events (low-quality evidence), myocardial infarction, stroke, thromboembolism (all high-quality evidence)). High-quality evidence shows that the liberal transfusion threshold did not affect the risk of infection (pneumonia, wound infection, or bacteraemia). Transfusion-specific reactions are uncommon and were inconsistently reported within trials.

We noted less certainty in the strength of evidence to support the safety of restrictive transfusion thresholds for the following predefined clinical subgroups: myocardial infarction, vascular surgery, haematological malignancies, and chronic bone-marrow disorders.

Authors' conclusions

Transfusion at a restrictive haemoglobin concentration decreased the proportion of people exposed to RBC transfusion by 41% across a broad range of clinical contexts. Across all trials, no evidence suggests that a restrictive transfusion strategy impacted 30-day mortality, mortality at other time points, or morbidity (i.e. cardiac events, myocardial infarction, stroke, pneumonia, thromboembolism, infection) compared with a liberal transfusion strategy.

Despite including 17 more randomised trials (and 8846 participants), data remain insufficient to inform the safety of transfusion policies in important and selected clinical contexts, such as myocardial infarction, chronic cardiovascular disease, neurological injury or traumatic brain injury, stroke, thrombocytopenia, and cancer or haematological malignancies, including chronic bone marrow failure.

Further work is needed to improve our understanding of outcomes other than mortality. Most trials compared only two separate thresholds for haemoglobin concentration, which may not identify the actual optimal threshold for transfusion in a particular patient. Haemoglobin concentration may not be the most informative marker of the need for transfusion in individual patients with different degrees of physiological adaptation to anaemia. Notwithstanding these issues, overall findings provide good evidence that transfusions with allogeneic RBCs can be avoided in most patients with haemoglobin thresholds between the range of 7.0 g/dL and 8.0 g/dL. Some patient subgroups might benefit from RBCs to maintain higher haemoglobin concentrations; research efforts should focus on these clinical contexts.

PLAIN LANGUAGE SUMMARY

Is it safe to use lower blood counts (haemoglobin levels) as a trigger for blood transfusion in order to give fewer blood transfusions?

Key messages

•There is no evidence that giving blood transfusions to patients with lower blood counts (haemoglobin levels of 7.0 g/dL to 8.0 g/dL) compared to higher blood counts (9.0 g/dL to 10.0 g/dL) affects risks of death, heart attack, myocardial infarction, stroke, pneumonia, blood clots or infection.

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• Giving blood only to patients with lower blood counts (7.0 g/dL to 8.0 g/dL) would reduce the amount of blood transfused substantially. It would also reduce the risk of unnecessary transfusions (transfusions can have harmful effects).

• More research is needed to:

- establish the blood count at which a blood transfusion is needed in people who have suffered a heart attack, brain injury, or have cancer; and to

- improve our understanding of outcomes other than death, including quality of life.

What happens in people who need blood transfusions?

Doctors and healthcare professionals often give blood transfusions to people who lose blood through surgery, bleeding, or illness. For example, blood transfusions may help patients with anaemia to recover after surgery, but they should only be given when they help people to get better from their medical condition. Blood is a limited resource and transfusion is not risk-free, especially for people in low-income countries where the blood used in transfusions may not be tested for harmful viruses such as HIV or hepatitis.

What did we want to find out?

The blood count measures the amount of haemoglobin in the blood. Haemoglobin is a protein that gives blood its red colour and carries oxygen around the body. A normal blood count is around 12 grams a decilitre (12 g/dL). We wanted to find out if it is safe to withhold blood transfusion until the blood count drops to between 7.0 g/dL to 8.0 g/dL, rather than transfusing sooner at higher blood counts of between 9.0 g/dL to 10.0 g/dL.

What did we do?

We examined the results of studies that allocated patients to one of two groups by chance (for example, by flipping a coin). In one group, the patients only received blood transfusions if their blood count fell below a higher threshold (typically, 9.0 g/dL to 10.0 g/dL). In the other group, the patients only received blood transfusions if their blood counts fell below a lower threshold (typically, 7.0 g/dL to 8.0 g/dL).

What did we find?

We found 48 studies that involved 21,433 patients. The patients had been hospitalised for a range of reasons including: bone (orthopaedic), heart (cardiac) or vascular surgery; critical care; acute blood loss (for example, through bleeding in the stomach or intestines); heart diseases; cancer and blood cancers. The studies compared higher or lower blood count thresholds for blood transfusion. (The 'threshold' is the blood count level that would need to be met before a transfusion would be given.)

Transfusion

We found that patients who received transfusions only at lower blood count thresholds were 41% less likely to receive a blood transfusion than those who received them only at higher blood count thresholds. If the lower threshold were applied routinely by medical staff, it would lead to a substantial reduction in the quantity of blood needed.

Death and harmful events

There was no clear difference in the risk of dying within 30 days of receiving, or not receiving, a transfusion for patients in the two different threshold groups.

There was also no clear difference between the low and high threshold groups for the number of serious harmful events that occurred after patients received, or did not receive, blood transfusions. The harmful events recorded included infection (pneumonia, wound infection, and blood poisoning), heart attacks, strokes, and problems with blood clots.

What are the limitations of the evidence?

We found that most of the studies provided a high quality of evidence; they were adequately conducted and used methods that minimised biases that could make the validity of the results uncertain.

We are confident in the evidence regarding likelihood of receiving a transfusion, death within 30 days of transfusion, heart attack, stroke and infection. We are moderately confident in the evidence for problems caused by blood clots, but too few occurred in either group for us to be more confident.

Too few studies evaluated quality of life for us to be able to see whether it varied between groups.

How up to date is this evidence?

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This Cochrane Review updates our previous work on this subject (last published in 2016). Seventeen new studies are included. The evidence is up to date to November 2020.

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Summary of findings 1. Liberal compared with restrictive transfusion protocols for guiding red blood cell transfusion

Liberal compared with restrictive transfusion protocols for guiding red blood cell transfusion

Patient or population: adults and children (haemodynamically stable) with potential need for RBC transfusion
Setting: inpatients
Intervention: restrictive transfusion threshold
Comparison: liberal transfusion threshold

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with liberal transfusion protocol	Risk with restrictive transfusion protocol				
Participants exposed to blood transfusion (all studies)	Study population		RR 0.59 (0.53 to 0.66)	20,057 (42)	⊕⊕⊕⊕ High	
	815 per 1000	481 per 1000 (432 to 538)				
30-Day mortality	Study population		RR 0.99 (0.86 to 1.15)	16,729 (31)	⊕⊕⊕⊕ High	
	83 per 1000	83 per 1000 (71 to 96)				
Myocardial infarction	Study population		RR 1.04 (0.87 to 1.24)	14,370 (23)	⊕⊕⊕⊕ High	
	32 per 1000	33 per 1000 (28 to 40)				
Congestive heart failure	Study population		RR 0.83 (0.53 to 1.29)	7247 (16)	⊕⊕⊖⊖ Low[a]	
	35 per 1000	29 per 1000 (19 to 45)				
Cerebrovascular accident - stroke	Study population		RR 0.84 (0.64 to 1.09)	13,985 (19)	⊕⊕⊕⊕ High	
	17 per 1000	14 per 1000 (11 to 19)				
Rebleeding	Study population		RR 0.80 (0.59 to 1.09)	3412 (8)	⊕⊕⊕⊖ Moderate[b]	
	158 per 1000	126 per 1000				

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		(93 to 172)			
Thromboembolism	Study population		OR 1.11 (0.65 to 1.88)	4201 (13)	⊕⊕⊕⊖ Moderate[c]
	15 per 1000	17 per 1000 (10 to 28)			
Infection	Study population		RR 0.97 (0.88 to 1.07)	17,104 (25)	⊕⊕⊕⊕ High
	143 per 1000	139 per 1000 (126 to 153)			

*__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; **OR:** odds ratio; **RBC:** red blood cell; **RR:** risk ratio

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded once for inconsistency, as there was no consistency in the direction of the effect (despite the relatively low statistical heterogeneity), and we downgraded once for imprecision, as there were very low numbers of events.
[b]Despite relatively low statistical heterogeneity, there was no consistency in the direction of the effect, hence we downgraded once for inconsistency.
[c]Downgraded once for imprecision, as there were few events (and hence a wide CI).

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BACKGROUND

Description of the condition

Patients who are ill in hospital are frequently anaemic, with low haemoglobin concentrations. The causes of anaemia are diverse, including loss of blood from surgery, bleeding, excessive blood sampling for laboratory tests, or as a consequence of illness. Additionally, patients with cancer may develop anaemia because the underlying disease, or chemotherapy, affects production of red cells in their bone marrow. Anaemia both decreases the oxygen content of blood supplied to the tissues, including the myocardial muscles of the heart, and increases myocardial oxygen demand by requiring higher cardiac output to maintain adequate oxygen delivery throughout the body (Sabatine 2005).

It is well known that anaemia is linked with multiple clinical symptoms; it is also associated with worse outcomes among patients who are anaemic before and after surgery or critical illness, or who have cardiovascular disease (Carson 1996; Kunz 2020; Shander 2014). However, it does not necessarily follow that correction of anaemia will improve outcomes, whether by red blood cell (RBC) transfusions (addressed in this review) or by alternative treatments such as intravenous iron (Richards 2020). Anaemia is generally well tolerated by many people, therefore, the benefits of administering potentially corrective treatments such as red cell transfusion need to be weighed against the risks.

Description of the intervention

The main treatment option for raising the haemoglobin concentration rapidly in patients with anaemia is RBC transfusion. RBCs for transfusion are collected from whole blood donations from blood donors. These are centrifuged to concentrate them before they are added to anticoagulant and storage solutions. Autologous transfusions, which are collected from and stored for the same individual, are not indicated for sicker hospitalised patients with anaemia.

Red cell transfusions are life-saving for patients with major bleeding. Red cell transfusions will treat severe anaemia successfully and may reduce the risks of major complications related to severe anaemia, such as myocardial infarction and heart failure. Uncertainties about the role of red cell transfusions are less clear for patients with less severe degrees of anaemia, and this is the focus of this review.

There are recognised risks of blood transfusion, as with any medical intervention (Delaney 2016). These risks, and the general availability of RBC transfusion vary throughout the world. In countries with well-regulated blood supplies and effective blood donor screening policies, the safety of allogeneic red cell transfusion has improved significantly over the past 30 years, and overall risks are very low. These risks continue to be well monitored through national haemovigilance systems (e.g. the UK's Serious Hazards of Transfusion; SHOT Annual Report 2019), which document very few cases of transfusion-transmitted infection; these findings reinforce earlier data from many countries (Zou 2009; Zou 2010). In resource-limited countries, the supply of blood remains inadequate, with highly variable rates of donation per 1000 individuals. Furthermore, blood may not be as safe in these countries as it is in resource-rich countries because it is not tested rigorously, and countries may lack quality control for viral pathogens, specifically transfusion-transmissible infections such as HIV, hepatitis B, hepatitis C, and syphilis (WHO 2016). In some resource-limited countries, a significant proportion of the blood supply is collected from family or paid blood donors - not from voluntary unpaid donors - and donor screening policies may not be efficiently applied. The prevalence of diseases such as HIV can be higher in low-income countries than in high-income countries, which presents a risk for transfusion transmission. All these points are described in the latest report on Global Blood Safety and Availability produced by the Blood Transfusion Safety Programme in the World Health Organization (WHO) Department of Service Delivery and Safety (WHO 2016).

Other risks of transfusion that have been described include acute transfusion reactions, volume overload, and transfusion-related acute lung injury (Delaney 2016; SHOT Annual Report 2019; Toy 2012). Less well-defined, but potentially important, adverse effects include loss of red cell nitric oxide production, which is thought to induce local vasodilatation; pro-thrombotic effects from factors in the supernatant or changes in blood viscosity following transfusions; and immunomodulatory (or pro-inflammatory) effects of different cellular products in the red cell component (Youssef 2017). Such harmful effects of RBC transfusions may be manifested, for example, as increased risks of infection (Rohde 2014).

Blood transfusion is expensive when one considers that around two million components (of which 1.6 million are units of RBCs) are issued across the UK alone each year (www.shotuk.org). The direct cost of each collected bag of red cells fails to capture the many associated costs related to hospital blood-banking practice and safe patient administration (Stokes 2018). In 2008, the mean payment for one unit of leuco-reduced RBCs in the USA was USD 223 (Whitaker 2011). However, when costs of administration as well as acquisition expenses of RBC transfusion were considered, the estimated cost derived from four USA and European hospitals rose to USD 761 per unit (standard deviation ± USD 294) (Shander 2010).

The impact of the storage age of red cells has been addressed in other systematic reviews (Shah 2018; Steiner 2015; Trivella 2019). Treatment options other than red cell transfusions for anaemia include erythropoietin and oral, or intravenous, iron therapy, which have been the topics of other recent trials and reviews (Richards 2020; Roman 2020).

How the intervention might work

The main clinical rationale for transfusing RBCs in anaemic patients is to improve oxygen delivery to tissue beds and vital organs such as the myocardium and brain. Transfusions may reduce compensatory work done by the heart to increase cardiac output in the face of anaemia. These benefits may manifest as better functional activity in patients and, ultimately, improved survival. Red blood cell transfusion is one of the few readily available treatments that consistently raises haemoglobin concentration and may restore tissue oxygenation adequately when oxygen demand exceeds supply (Wang 2010).

There is a long history of randomised controlled trials that have compared outcomes for participants allocated to different policies or schedules of red cell transfusion; these have now been completed and reported (Mueller 2019; NIH 1988). These studies presented results after randomising participants to either

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'restrictive' triggers (where, typically, participants are transfused only when their haemoglobin concentration falls below 7.0 g/dL to 8.0 g/dL) or 'liberal' triggers (where participants are transfused at a higher haemoglobin concentration of around 9.0 g/dL to 10.0 g/dL). Historically, the widely accepted clinical standard was to transfuse patients when haemoglobin level dropped below 10.0 g/dL or when haematocrit fell below 30% (Wang 2010). Many guidelines based on the evolving evidence base now recommend that a range of haemoglobin values between 6.0 g/dL to 10.0 g/dL can be safely used for directing transfusions, depending on the presence of serious comorbidity (AAGBI 2008; ASA 2006; Carson 2012a; Carson 2016a; Mueller 2019; Napolitano 2009).

Why it is important to do this review

Much of the earlier evidence comparing restrictive and liberal thresholds for red cell transfusion comes from trials based in critical care. In 1999, the landmark TRICC trial (**t**ransfusion **r**equirements **i**n **c**ritical **c**are) reported similar mortality in participants transfused at a restrictive trigger less than 7.0 g/dL compared with a liberal trigger less than 10.0 g/dL (Hébert 1999). The number of randomised trials continues to expand, as has been reported in previous iterations of this Cochrane Review (Carless 2010b; Carson 2012b; Hill 2000; Hill 2002; Hill 2005). By 2012, the number of participants enrolled in trials had doubled from 6264 to 12,587 (Carson 2012b); this number rose to 19,049 participants in a targeted update published in 2018, which specifically focused on patients with cardiovascular disease (Carson 2018). As further new trials continue to be published, there remains an ongoing need to update this systematic review, to ensure that new and updated guidelines on the use of red cell transfusions are based on the most recent literature reports of the effectiveness and safety of RBC transfusion (Carson 2016a). In addition, new studies focus on relevant and specific clinical contexts, for which previous levels of evidence for supporting best practice were very limited. This allows this updated review to inform transfusion practice in relevant subpopulations of patients.

The purpose of this updated review was to identify, appraise, and summarise the data from all randomised controlled trials (RCTs) that studied the clinical impact of varying thresholds for transfusion with RBCs. We remain interested in whether results of RCTs support the trend for increasingly restrictive RBC transfusion practices across different trial settings without harm to patients and to what extent RBCs need to be given more liberally in selected patient subgroups.

OBJECTIVES

The aim of this review update was to compare 30-day mortality and other clinical outcomes for participants randomised to restrictive versus liberal red blood cell (RBC) transfusion thresholds (triggers) for all clinical conditions. The restrictive transfusion threshold uses a lower haemoglobin concentration as a threshold for transfusion (most commonly, 7.0 g/dL to 8.0 g/dL), and the liberal transfusion threshold uses a higher haemoglobin concentration to direct transfusion (most commonly, 9.0 g/dL to 10.0 g/dL).

METHODS

Criteria for considering studies for this review

Types of studies

To examine evidence for the effects of transfusion thresholds on the use of red blood cell (RBC) transfusions and evidence for any change in clinical outcomes, we included randomised controlled trials (RCTs) in which comparison groups were assigned on the basis of a transfusion 'threshold' (sometimes termed a 'trigger'), defined as haemoglobin concentration or haematocrit level (with or without a specified level of haemodynamic instability) that had to be reached before RBC transfusion was administered. We required trials in which groups of participants were transfused with RBCs at higher haemoglobin or haematocrit levels (transfusion threshold) than those in a lower transfusion group, or were compared to those transfused in accordance with current standard transfusion practices. We excluded trials that were not designed to include any clinical outcomes relevant to this review.

Types of participants

We included trials of surgical or medical participants, involving adults or children, or both. We excluded studies enrolling neonates, given the distinct pathophysiology and clinical features of neonate anaemia, which is the topic of a separate Cochrane Review (Whyte 2011).

Types of interventions

The intervention considered was use of transfusion thresholds ('triggers') as a means of guiding allogeneic or autologous RBC transfusion, or both. A liberal transfusion threshold most often refers to transfusion of blood when the haemoglobin level falls below 9.0 g/dL to 10.0 g/dL. A restrictive transfusion threshold most often refers to transfusion of blood when the haemoglobin level falls below 7.0 g/dL to 8.0 g/dL.

We also included trials that compared transfusion and no transfusion while defining the no transfusion group as the restrictive strategy. Such trials may define a second threshold as a lower limit under which participants' haemoglobin should not fall without initiation of transfusion; this is consistent with all other trials in which clinical discretion is allowed for severe symptomatic anaemia.

Types of outcome measures

We evaluated clinical outcomes for efficacy, and we assessed complications of transfusion for safety.

Primary outcomes

The primary outcome for the analysis was 30-day mortality. Mortality is a clinically relevant outcome that is widely cited in studies including patients with acute illness, critical illness, and perioperative care.

Secondary outcomes

We examined three categories of secondary outcomes:

- mortality at different time intervals;
- morbidity outcomes;
- subgroups for mortality and morbidity.

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We recorded and analysed mortality at different time points, including during hospital admission, at 90 days, and over the long term (median follow-up, 3.1 years).

We evaluated morbidity that occurred during hospitalisation, including cardiac events (both as a composite outcome that included myocardial infarction, cardiac arrhythmias, cardiac arrest, pulmonary oedema, and angina, and individually when feasible), non-fatal and fatal myocardial infarction, congestive heart failure, cerebral vascular accident (stroke), rebleeding, infection, thromboembolism, renal failure, mental confusion, function, and fatigue.

Infection was defined in three ways: sepsis or bacteraemia, pneumonia alone, or pneumonia plus wound infection. For the 2021 update, we added a specific outcome of 'transfusion-specific reactions', as defined and reported in included studies. These events are uncommon, but they are important.

We defined all morbidity outcomes according to the definitions provided in individual trials. We evaluated subgroups based on transfusion thresholds and clinical context.

We recorded information on quality of life and functional outcomes. We also compared use of RBC transfusion as a measure of implementation of the transfusion intervention between groups by proportions of participants exposed to transfusion, units of blood transfused, and mean haemoglobin levels.

As this review is an update, we have continued to include some of these secondary outcomes for historical reasons. As stronger evidence is accrued, we believe that in future updates of this review, reporting of some of these outcomes may need to be modified or omitted.

Search methods for identification of studies

Electronic searches

We searched the following databases and ongoing trial registries:

- CENTRAL (Cochrane Central Register of Controlled Trials; 2020, Issue 11), in the Cochrane Library (www.cochranelibrary.com);
- MEDLINE via OvidSP (from 1946 to 16 November 2020);
- Embase via OvidSP (from 1974 to 16 November 2020);
- PubMed (for e-publications ahead of print only, on 16 November 2020);
- Transfusion Evidence Library (www.transfusionevidencelibrary.com; 1950 to 16 November 2020);
- Web of Science Conference Proceedings Citations Index (CPCI-S, 1990 to 16 November 2020);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched to 16 November 2020);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched to 16 November 2020).

We combined searches in MEDLINE and Embase with adaptations of the Cochrane RCT search filter as detailed in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We did not restrict our search by date, language, or publication status. We present search strategies for the 2012 update in Appendix 1, for the 2016 update and trial registries in Appendix 2 and Appendix 3, respectively, and for the 2020 update in Appendix 4.

Searching other resources

We checked the references of all identified trials, relevant review articles, and current treatment guidelines for further literature. We limited these searches to 'first-generation' reference lists (i.e. reference lists of papers retrieved directly by database searches).

We contacted experts in the field to identify information relevant to the review. When possible and when necessary, we contacted authors of published studies for clarification of trial methods and data. We emailed all authors of trials that did not report our primary outcome of 30-day mortality, but this was not possible for older trials for which contact information was not available. We searched the reference lists of relevant reviews and transfusion trials.

Data collection and analysis

Selection of studies

Two review authors (JLC and SJS) independently screened the titles or abstracts of the search results, or both, and selected trials that met the inclusion criteria. We resolved disagreements by discussion until we reached consensus. We identified trials in which participants were randomised to a restrictive transfusion strategy (transfusion threshold or protocol, or both) or to a control group that was randomised to a liberal transfusion strategy.

Data extraction and management

JLC and Paul Carless (a prior review author) extracted all data for earlier versions of this review. For this 2021 update, JLC and SJS independently extracted study characteristics and outcomes of new trials added since the last review, using a data extraction form. Information recorded on the extraction form included study type, presence of a transfusion threshold, transfusion protocol, type of surgery involved, clinical setting, treatment outcomes, and general comments, as well as details relevant to assessment of risk of bias for key domains described below. JLC entered data into Review Manager 5.4; NR checked data; JD added new items into tables to meet contemporary MECIR (Methodological Expectations for Cochrane Intervention Reviews) standards, which were checked by both JLC and SJS. We contacted authors of trials to request missing data.

We used the data extraction form to record data on the following outcomes:

- number of participants exposed to allogeneic blood;
- amount of allogeneic blood transfused;
- number of participants receiving any transfusion (allogeneic blood, autologous blood, or both).

For trials involving surgical participants, we recorded the following:

- postoperative complications (infection, haemorrhage, non-fatal myocardial infarction, cardiac events, renal failure, stroke, thromboembolism, pulmonary oedema, mental confusion);
- mortality, blood loss, haemoglobin and haematocrit levels (on admission, pre- and post-transfusion, and at discharge);

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- demographics (age, sex);
- type of surgery; and
- medical condition.

We extracted data for allogeneic blood transfusion if it was expressed as packed RBCs. We documented information regarding the use of fresh frozen plasma or platelets, or both.

Assessment of risk of bias in included studies

We used the Cochrane tool for assessing risk of bias as described in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

JLC, SJS, and JD assessed the following domains for each study:

- sequence generation;
- allocation concealment;
- blinding (assessments were made separately with regard to objective (e.g. mortality) and subjective (e.g. self-reported quality of life) outcomes);
- incomplete outcome data;
- selective outcome reporting; and
- other potential sources of bias.

We completed a risk of bias table for each trial, incorporating a description of the trial's performance against each of the above domains and our overall judgement of the risk of bias for each entry as follows: 'low', 'unclear' (indicating unclear or unknown risk of bias), or 'high' risk of bias.

Measures of treatment effect

We obtained the risk ratio (RR) for allogeneic blood transfusion in the intervention group compared with the control group and corresponding 95% confidence intervals (CIs) for each trial. We adopted a similar approach for other outcomes of transfusion. When the event rate was low, we considered using the Peto odds ratio when criteria for this method were fulfilled. We also entered the mean number of units of RBCs transfused to each group and the corresponding standard deviations. We used the mean difference (MD) and 95% CI to express average mean reduction in the number of units of RBC administered to the intervention group compared with the control group.

Unit of analysis issues

The unit of analysis was the participant. In all trials except one (Jairath 2015), randomisation was done at the individual participant level. In this trial in people with gastrointestinal bleeding, randomisation was done at the level of the hospital (cluster), but analysis occurred at the level of the individual participant. The intraclass correlation coefficient (ICC) was very low (0.0001) for the outcome of mortality; therefore we included the data and considered the participant as the unit of randomisation and ignored the clustering. We performed a sensitivity analysis from which we excluded this trial, to see what effect, if any, this had on the analysis. We did not evaluate any outcomes with repeated measures.

Dealing with missing data

We performed all analyses on an intention-to-treat basis. We undertook no imputations for missing data. We received information on 30-day mortality from three authors (DeZern 2016; Villanueva 2013; Webert 2008). Levels of missing data were never higher than 10%, which we consider acceptable.

Assessment of heterogeneity

We examined statistical heterogeneity using both the I^2 statistic and the Chi^2 test. The I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; moderate or substantial heterogeneity is considered to exist when I^2 exceeds 50% or 85%, respectively (Higgins 2011). For the Chi^2 test, we used a P value < 0.10 to indicate the presence of statistically significant heterogeneity. Because of the anticipated significant clinical heterogeneity of trials, we analysed data using a random-effects model. We also anticipated a high level of heterogeneity related to transfusion rates because practice in the different specialties of the trials would vary considerably according to specialty-specific protocols. Therefore, as described later, we chose to provide a summary statistic for the outcomes of transfusion even when I^2 was very high, because of the clinically relevant information this provides.

Assessment of reporting biases

When more than 10 studies were available, we examined funnel plots for the primary outcome of 30-day mortality and the proportion of participants transfused, to assess the potential for publication bias. We used the proportion of participants transfused because all trials reported this outcome, and this may reflect overall risk of publication bias better than 30-day mortality, which was not reported in all of the trials. We sought evidence of selective outcome reporting by comparing plans from described registrations/protocols (when available) with final reports.

Data synthesis

We performed all analyses using Review Manager 5.4 software (Review Manager 5a). We entered data for numbers of participants exposed to red cell transfusions, anticipated to be allogeneic blood in most trials and patients. We present the results using haemoglobin concentration in grams per decilitre (g/dL). Based on study reporting, we converted haematocrit to haemoglobin concentration by dividing by three. When studies presented transfusion volume as millilitres (mL), we converted these amounts to units by dividing by 300 (as in most countries, a standard unit of red blood cells is 300 mL). We pooled data for all outcomes and presented data stratified by subgroups for the primary outcome of 30-day mortality and proportion of participants transfused by using a random-effects model (Der Simonian 1986), and we presented the pooled result along with its 95% CI. We used Peto odds ratios for outcomes with event rates less than 1%. For continuous variables, we estimated the pooled mean difference and the 95% CI by using the generic inverse variance method.

Subgroup analysis and investigation of heterogeneity

Prespecified subgroups, as established in prior reviews, consisted of the following clinical contexts:

- acute blood loss/trauma;
- cancer;
- cardiac surgery;

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- critical care;
- orthopaedic surgery;
- myocardial infarction;
- vascular surgery; and
- haematological malignancy.

We examined 30-day mortality and the proportion of participants exposed to transfusion stratified by the transfusion threshold (difference between liberal and restrictive transfusion thresholds: ≥ 2.0 g/dL and < 2.0 g/dL; and restrictive transfusion threshold < 7.0 g/dL versus one of 8.0 g/dL to 9.0 g/dL). We also examined a post hoc subgroup of enrolled participants with myocardial infarction compared with all other clinical specialties, and we combined cardiac surgery with myocardial infarction because of emerging evidence that participants with acute myocardial infarction might differ from other anaemic participants (Carson 2013).

For the primary outcome of 30-day mortality, we also compared findings between prospectively registered trials and those that were unregistered, or were registered long after recruitment began. Blood components are not subject to the same legal requirements for prospective registration as medical devices or pharmaceutical interventions. As in prior versions of this review, we did not exclude unregistered trials published after 2010 (as per the Cochrane Injuries Group policy), and we did conduct analyses to consider differential impact of the results of all trials for which proof of prospective registration could (or could not) be confirmed.

Sensitivity analysis

We performed a sensitivity analysis to assess effects of studies with high risk of bias for allocation concealment for the primary outcome; however, as in earlier versions of the review, sensitivity analyses for secondary outcomes were not informative. We repeated the analysis while excluding the cluster randomised trial (Jairath 2015).

Summary of findings and assessment of the certainty of the evidence

We have presented judgements about the quality of evidence in a summary of findings table (according to guidelines developed by the GRADE Working Group) (Schünemann 2011). We rated the quality of evidence as 'high', 'moderate', 'low', or 'very low', according to the following five GRADE domain considerations of: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

This table includes the following outcomes:

- number of people receiving blood transfusions;
- 30-day mortality;
- myocardial infarction;
- congestive heart failure;
- cerebrovascular accident (stroke);
- rebleeding; and
- thromboembolism.

RESULTS

Description of studies

Details of the selection process for, and characteristics of, the included studies are offered below, along with information about interventions and trial design.

Results of the search

See Figure 1 for the PRISMA flowchart describing trial selection for the present update.

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Figure 1. Flow of studies for 2021 update

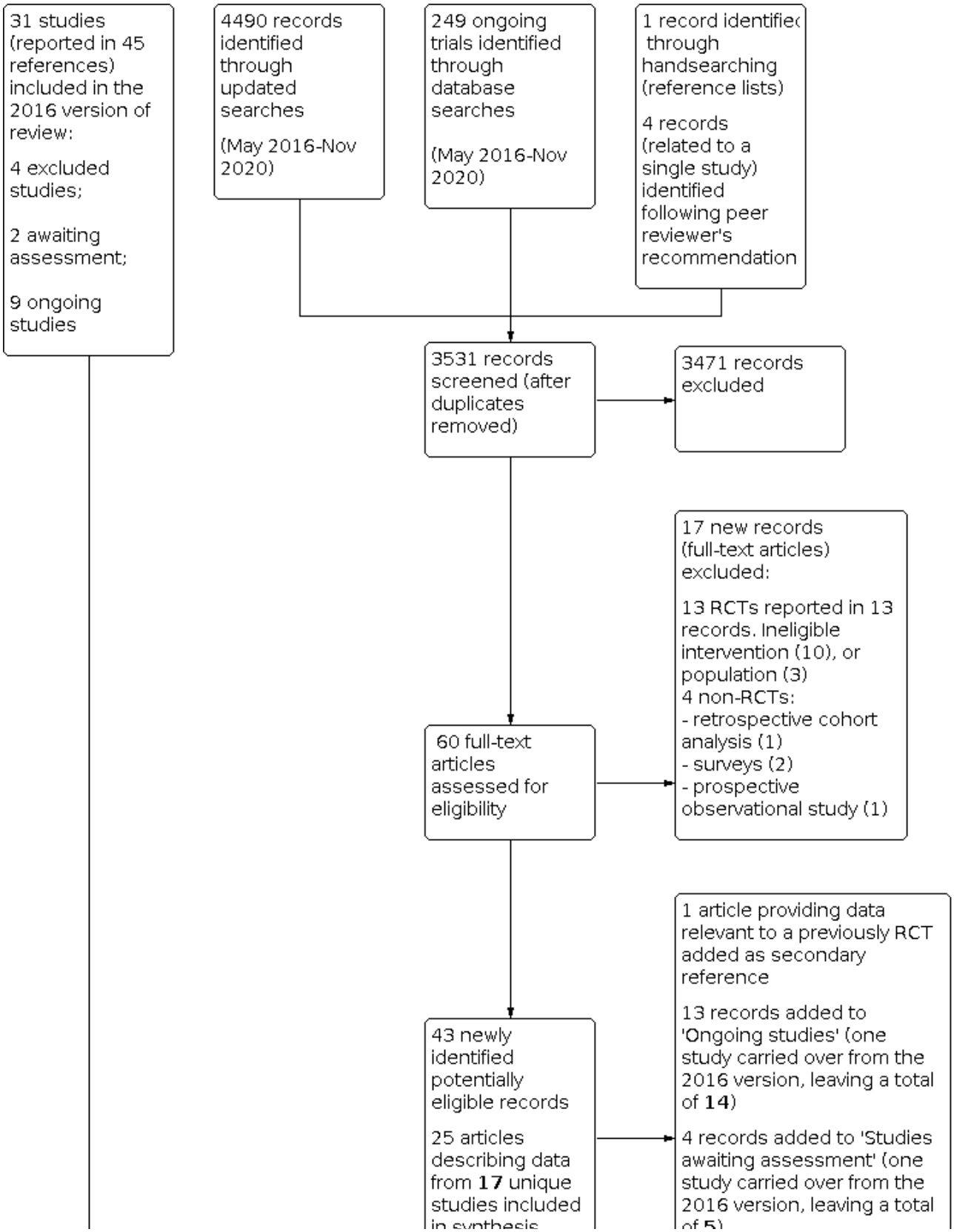

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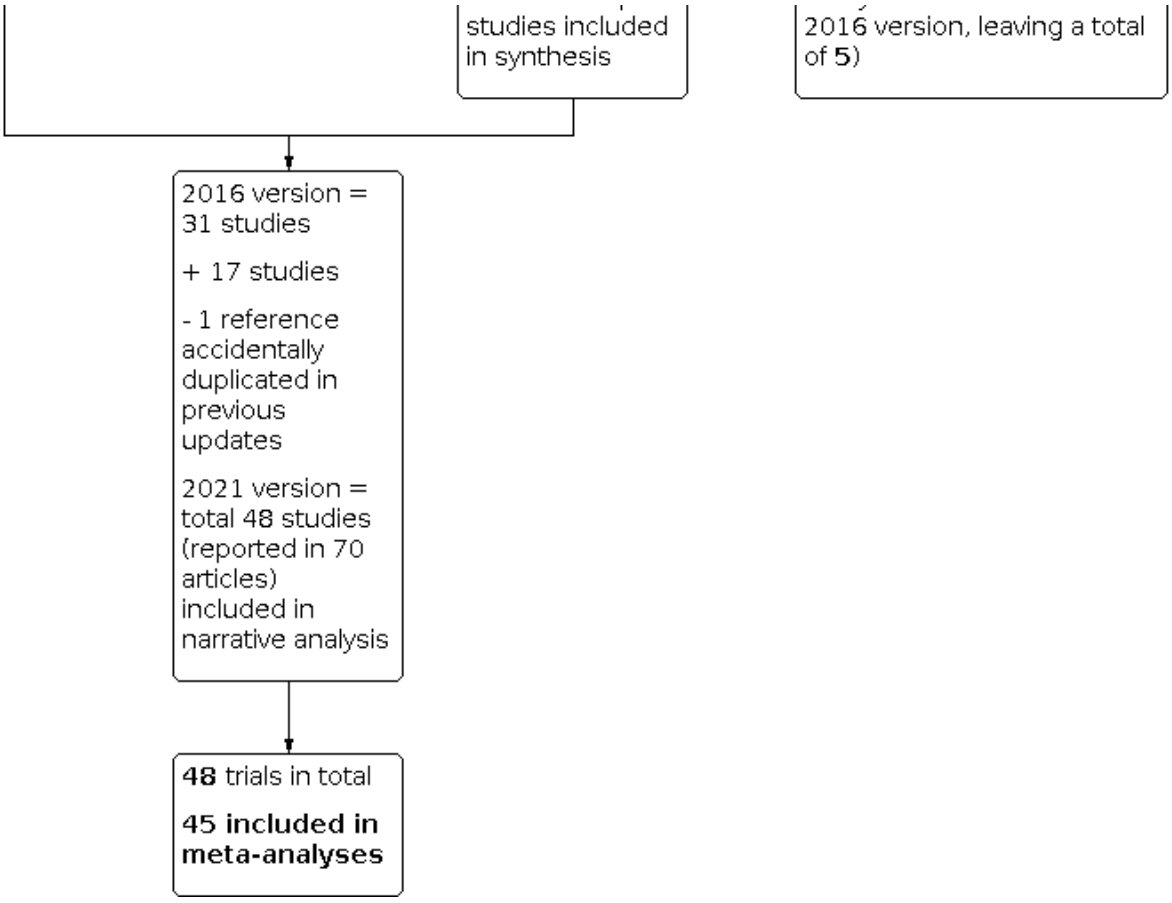
Figure 1. (Continued)



In the previous review, published in 2016, we included 31 studies.

For this 2021 update, we identified and analysed 17 additional trials (Akyildiz 2018; Bergamin 2017; Ducrocq 2021; Gillies 2020; Gobatto 2019; Hoff 2011; Jansen 2020; Koch 2017; Kola 2020; Laine 2018; Mazer 2017; Møller 2019; Palmieri 2017; Robitaille 2013; Stanworth 2020; Tay 2020; Yakymenko 2018) (Figure 1), leading to a total of 48. We identified one of these trials - Ducrocq 2021 - as an ongoing trial when we searched trials registers in November 2020; it has subsequently been published and is included in the analysis. We reviewed eligibility for one analysis after peer review and included data from it only in a narrative synthesis (Hoff 2011). This analysis treated the outcomes of two linked studies (DAHANCA 5 and DAHANCA 7) as a single trial (Hoff 2011a; Hoff 2011b; Overgaard 1998; Overgaard 2003).

Many of the included trials have been reported within multiple papers, which are included as secondary references. Whilst the focus of this review was the main (first) report of outcome data, reports of secondary or subgroup analyses (e.g. long-term outcomes) occasionally offered complementary information useful for data extraction and assessment of bias.

Included studies

Participants

This updated systematic review includes a total of 21,433 trial participants (at baseline) across 48 trials described in 70 publications. By comparison, in the 2016 Cochrane review (Carson 2016b), we reported on an analysis of 31 trials that enrolled 12,587 participants.

The clinical context of the 48 trials was varied:

- 11 studies involved orthopaedic surgery (Carson 1998; Carson 2011; Fan 2014; Foss 2009; Gillies 2020; Gregersen 2015; Grover 2005; Lotke 1999; Nielsen 2014; Parker 2013; So-Osman 2013);
- seven involved critical care (de Almeida 2015; Gobatto 2019; Hébert 1995; Hébert 1999; Holst 2014; Palmieri 2017; Walsh 2013);
- six examined acute blood loss (Blair 1986; Jairath 2015; Kola 2020; Prick 2014; Topley 1956; Villanueva 2013), four of which concerned gastrointestinal bleeding, one postpartum haemorrhage (Prick 2014), and one trauma (Topley 1956);
- eight included cardiac surgery (Bracey 1999; Hajjar 2010; Johnson 1992; Koch 2017; Laine 2018; Mazer 2017; Murphy 2015; Shehata 2012);
- three involved acute coronary syndrome (Carson 2013; Cooper 2011; Ducrocq 2021);
- eight involved cancer, leukaemia, and haematological malignancies (Bergamin 2017; DeZern 2016; Hoff 2011; Jansen 2020; Stanworth 2020; Tay 2020; Webert 2008; Yakymenko 2018);
- two were in vascular surgery (Bush 1997; Møller 2019);
- three enrolled paediatric participants (Akyildiz 2018; Lacroix 2007; Robitaille 2013). Two trials were conducted in paediatric

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intensive care units (Akyildiz 2018; Lacroix 2007), and one trial involved bone marrow transplant recipients (Robitaille 2013).

Interventions

We noted variation in the definitions of transfusion strategies specified in the protocols, but most commonly, haemoglobin concentrations were used as 'triggers'. Four trials specified haematocrit values for the threshold (Cooper 2011; Hajjar 2010; Koch 2017; Johnson 1992). Four trials incorporated symptoms in addition to haemoglobin threshold in the restrictive transfusion strategy (Carson 2011; Carson 2013; Parker 2013; Prick 2014).

Transfusion thresholds by haemoglobin concentration in restrictive transfusion arms (44 trials) varied from 7.0 g/dL to 9.7 g/dL. The most common restrictive haemoglobin threshold for interventions was between 7.0 g/dL to 8.0 g/dL (35 trials). Two trials recruited patients in the outpatient chronic transfusion-dependent population setting based on haemoglobin concentrations (Jansen 2020; Stanworth 2020), and thresholds for the intervention arms in these trials were higher, as might be expected for this population. Three trials defined a no-transfusion strategy for the 'restrictive' arm (Hoff 2011; Parker 2013; Prick 2014), with provisions made for participants with clear signs of anaemia.

Restrictive haematocrit varied between 24% and 25% (equivalent to haemoglobin levels of around 8 g/dL) (Cooper 2011; Hajjar 2010; Johnson 1992; Koch 2017).

The most common transfusion threshold by haemoglobin concentration in the liberal transfusion arm was 9.0 g/dL to 10.0 g/dL. However, the liberal transfusion threshold varied and included:

- 100% of 'normal red cell volume' (Topley 1956);
- two units of blood irrespective of clinical state (immediately in one trial (Blair 1986), postoperatively in another (Lotke 1999)); and
- transfusion sufficient to maintain haemoglobin levels:
  - above 10 g/dL (Gregersen 2015; Hoff 2011; Jansen 2020; Robitaille 2013; Stanworth 2020; Webert 2008; Yakymenko 2018);
  - at 10 g/dL (Bush 1997; Carson 1998; Carson 2011; Carson 2013; Ducrocq 2021; Foss 2009; Grover 2005; Hajjar 2010; Hébert 1995; Hébert 1999; Jairath 2015; Parker 2013);
  - at 9.5 g/dL (Lacroix 2007; Shehata 2012);
  - at 9 g/dL (Bergamin 2017; Bracey 1999; de Almeida 2015; Gillies 2020; Gobatto 2019; Holst 2014; Murphy 2015; Tay 2020; Villanueva 2013; Walsh 2013);
  - at 8.9 g/dL (Prick 2014); and
  - at 8 g/dL (DeZern 2016; Kola 2020; Møller 2019).

Four trials used haematocrit levels when determining triggers (Cooper 2011 and Hajjar 2010 specified the liberal triggers as haematocrit levels of 30%; Koch 2017 specified a level of 28%, and Johnson 1992 a level of 32%).

Trial setting and design

See Table 1.

The included studies were conducted at a total of nearly 400 sites within 26 countries. High-income countries including Canada, the UK, and the USA contributed the bulk of both single-site and multicentre studies, as well as co-ordinating international multicentre studies. The next most common countries, in terms of providing settings for eligible trials, were Denmark, the Netherlands, Brazil, and France. Recruitment start dates for studies included within this review ran between 1955 and 2017, with a marked increase in the rate of new studies commencing recruitment from 2009 onwards.

A total of 24 of the 48 included studies were unregistered or were registered by investigators long after recruitment began. Although a majority of unregistered trials were relatively old, lack of prospective registration is a problem that persists to the present day.

In 47 of the 48 trials, the participant was the unit of randomisation and analysis. One trial used cluster randomisation by hospital (Jairath 2015). Sample sizes of included studies varied enormously (from 6 to 5092 participants randomised at baseline). Twenty-six trials included 100 or more participants, and four trials included over 1000 participants each (Carson 2011; Holst 2014; Mazer 2017; Murphy 2015). Eleven of the included studies were described as pilot or feasibility studies (Carson 2013; DeZern 2016; Gillies 2020; Gobatto 2019; Hébert 1995; Jairath 2015; Møller 2019; Shehata 2012; Stanworth 2020; Webert 2008; Yakymenko 2018). We counted two linked studies in patients with head and neck squamous cell carcinoma before radiotherapy as one trial for the purpose of this review (Hoff 2011); the two component studies, DAHANCA 5 and DAHANCA 7, tested the same main trial intervention (nimorazole) and then applied a similar subrandomisation question to evaluate transfusion versus no transfusion, given concerns about poorer responses to radiation therapy due to a hypothesis of hypoxia-induced radio-resistance.

Excluded studies

In 2016, this review contained records of four excluded studies. In this 2021 update, we have excluded a further 17 studies; data for these studies were published in 22 publications (see Characteristics of excluded studies). Of the 21 excluded studies, 17 are ineligible RCTs (excluded largely on grounds of intervention or population); the remaining four are non-randomised studies of different designs.

Studies awaiting classification

Brief details of five trials that are awaiting assessment are shown in the Studies awaiting classification section. Four have been completed but remain unpublished; we are considering how to handle data reported in the fifth (published) trial, which was of a complex, multifactorial design.

Ongoing studies

Brief details of 14 ongoing studies identified from searches of international trial registers are shown in the Ongoing studies section. When completed, and if eligibility criteria remain stable, results from these studies may add data from approximately 14,880 participants to this review, with five trials aiming to recruit over 1000 participants each. The latter (larger) studies are focusing on populations that are currently under-represented in the studies included in this review, specifically, those with traumatic brain injury or cardiac/vascular disease.

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Risk of bias in included studies

The risk of bias tables detail the assessment of studies for each domain and are summarised in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included trials. Forty-eight trials are included in this review.

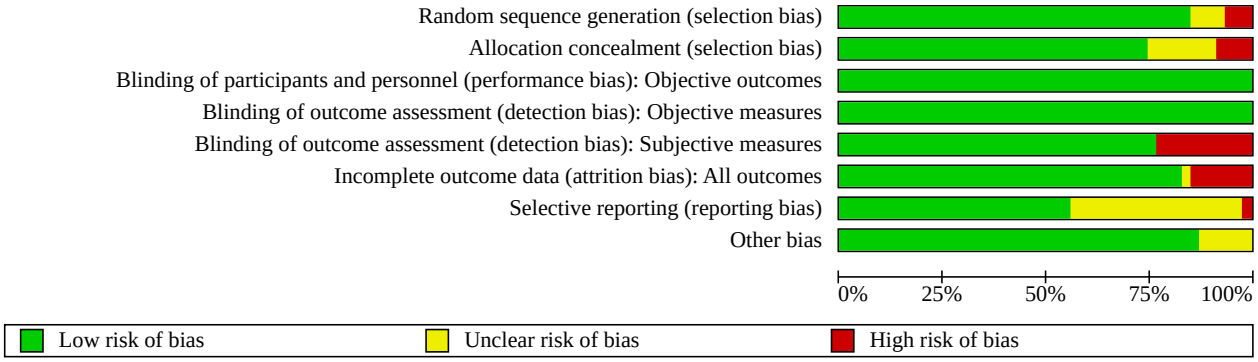

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Figure 3. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included trial

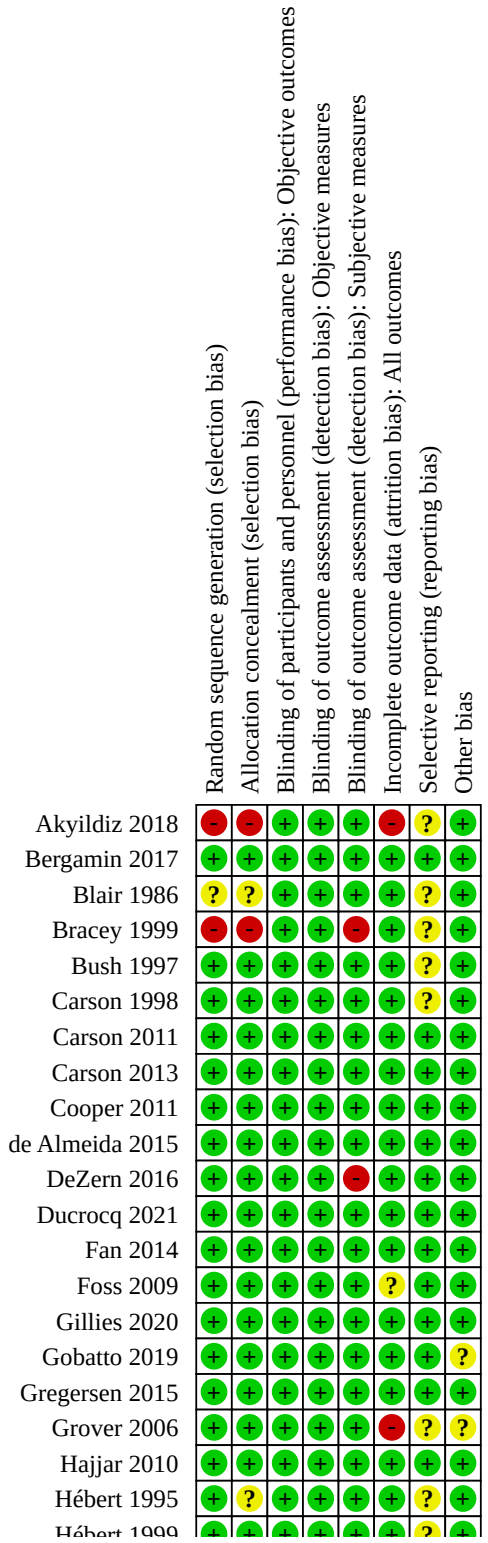

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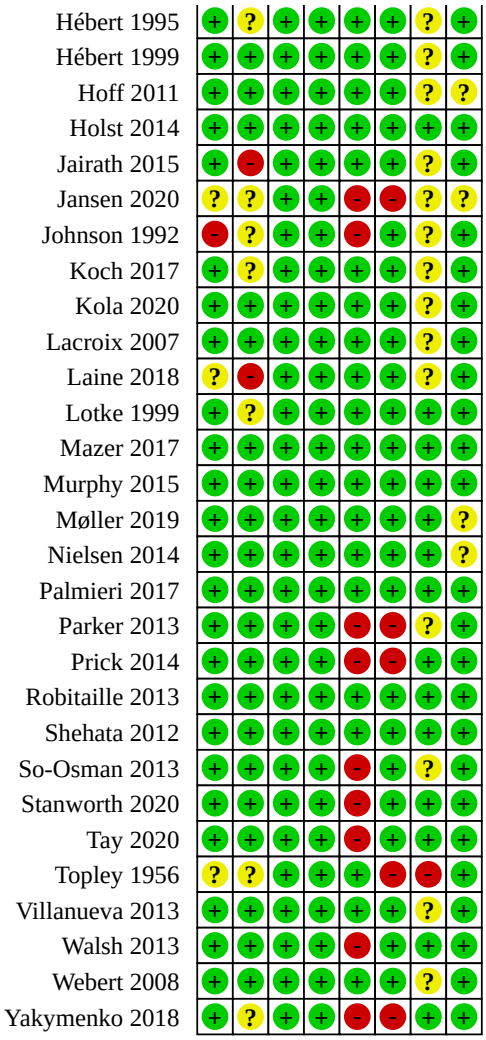
Figure 3. (Continued)



Allocation

Sequence generation

We judged 41 trials to be at low risk of bias for this domain. We judged three trials to be at high risk of bias: one for basing the randomisation sequence on hospital record number, one for using coin-tossing, and one because it mentioned using both a table of random numbers and odd/even (restrictive/liberal) allocation strategy. The remaining four trials presented insufficient information for us to be able to assess the adequacy of sequence generation, so we rated them as being at unclear risk.

Allocation concealment

We judged the risk of bias for this item to be low for 36 trials that used central allocation or sealed envelopes if appropriate safeguards (e.g. sequentially numbered envelopes) were used. We judged four trials to be at high risk of bias: one of these trials used a cluster design, so everyone in all hospitals knew to which group all participants had been assigned (Jairath 2015), one used a coin toss, one used hospital numbers that could be seen, and one used closed envelopes. We rated the risk for eight trials as unclear because the publications did not provide any information about how allocation was concealed.

Blinding

Performance bias

The nature of the intervention meant that blinding of clinicians involved in the care and administration of blood transfusions would not have been possible. Blinding of personnel for this intervention is also not feasible. In our view, for objective outcomes such as mortality (the primary outcome used within this review), it is appropriate to assess risk of bias as low.

Detection bias

Outcomes are assessed optimally when assessors are blinded to assignment. It is possible to blind the assessment of many outcomes by using, for example, an adjudication committee. In contrast, for some outcomes such as death, blinded assessment is less relevant. We classified risk of bias on the basis of the primary

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outcome of the trial (mortality) and on subjective outcomes, if reported, including functional measures and quality of life. We judged the risk of bias to be high for 11 trials for subjective outcomes.

Incomplete outcome data

We rated seven trials as being at high risk of bias for this domain, as data were missing for a large proportion of participants (20% to 45% of data for an outcome important to this review in six cases) or were missing disproportionately between arms (one trial).

Selective reporting

We rated 20 trials as being at unclear risk of bias for this domain, largely because evidence of prospective registration could not be confirmed. One trial (the oldest in the review, which recruited in the early 1950s) was assessed as being at high risk of bias for not reporting the groups in which deaths occurred. The remaining trials were assessed as having a low risk of bias for this domain.

Other potential sources of bias

We identified few other sources of bias. Small trials, including feasibility or pilot studies (which account for 20% of included trials), often reported small imbalances at baseline, as might be expected. Some trials were obliged to terminate prematurely due to slow recruitment. Only a limited number of trials described protocol violations for transfusions in detail, but these applied to both intervention arms. Overall, we assessed six of the 48 trials as having unclear risk of bias for this domain.

Effects of interventions

See: **Summary of findings 1** Liberal compared with restrictive transfusion protocols for guiding red blood cell transfusion

Substantial variation in outcomes was reported in the included trials, which, in part, reflects their clinical settings.

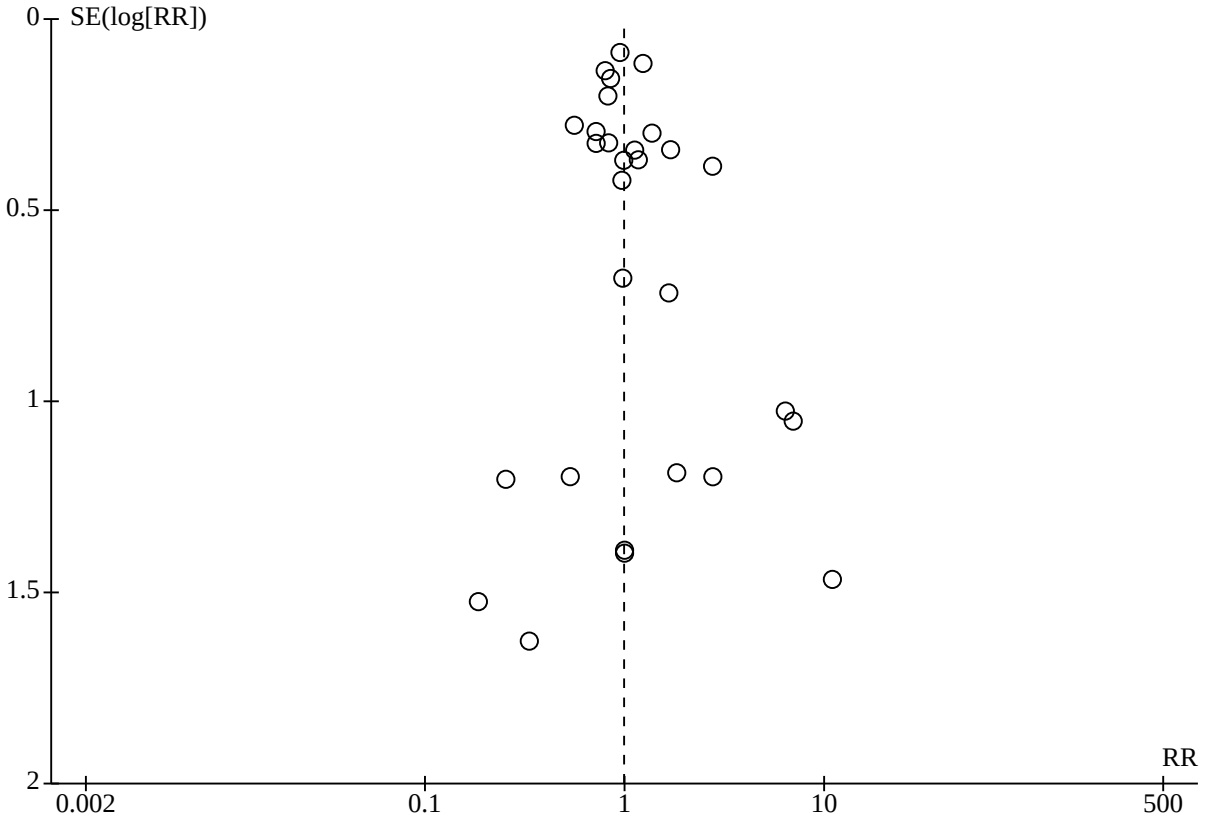
Nearly all trials contributed to the analysis comparing the proportion of participants transfused in liberal and restrictive transfusion groups. Despite the heterogeneous methods and transfusion triggers reported in these RCTs, it was possible to pool data, to varying degrees, for each of the review outcomes. See Summary of findings 1.

Primary outcome

30-Day mortality

The primary outcome of 30-day mortality was reported by 31 trials (including 16,729 participants) in a form suitable for meta-analysis. There was no difference in 30-day mortality between restrictive and liberal transfusion strategies (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.86 to 1.15; Analysis 1.1). Heterogeneity between these trials was not important (Chi^2 = 40.06, degrees of freedom (df) = 28 (P = 0.07); I^2 = 30%). The funnel plot demonstrates that the RR for 30-day mortality is symmetrically distributed, which indicates there is not likely to be publication bias for this outcome (Figure 4).

Figure 4. Funnel plot of comparison: 1 Mortality, outcome: 1.1 30-Day mortality



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Subgroup analysis of 30-day mortality: restrictive threshold of 7.0 g/dL to 7.5 g/dL versus 8.0 g/dL to 9.0 g/dL

We examined 30-day mortality and stratified it by the restrictive transfusion threshold used in the trials. Fifteen trials with 11,572 participants used a 7.0-g/dL restrictive threshold. The RR for 30-day mortality was 1.00 (95% CI 0.83 to 1.19; Analysis 1.2). Sixteen trials with 5157 participants used a restrictive threshold of 8.0 g/dL to 9.0 g/dL. The RR for 30-day mortality was 0.97 (95% CI 0.75 to 1.24; Analysis 1.2). The test for subgroup differences did not show any differences between subgroups (Chi^2 = 0.04, df = 1 (P = 0.83), I^2 = 0%), indicating there was no difference in the mortality risk between the two thresholds.

Subgroup analyses of 30-day mortality: clinical context

We examined 30-day mortality and stratified it by the clinical context used in the trials: cardiac surgery, orthopaedic surgery, vascular surgery, acute blood loss or trauma (analyses for this grouping for 30-day mortality included gastrointestinal (GI) bleeding only), critical care, acute myocardial infarction, and haematological malignancies. The overall RR for 30-day mortality stratified by clinical specialty was 0.99 (95% CI 0.86 to 1.14; 31 trials, 16,729 participants; Analysis 1.3). There were no differences in 30-day mortality between subgroups (Chi^2 = 6.73, df = 6 (P = 0.35); I^2 = 10.9%).

Cardiac surgery

Four trials conducted in 7411 patients undergoing cardiac surgery reported 30-day mortality. The RR for 30-day mortality for a restrictive compared to a liberal transfusion strategy was 0.99 (95% CI 0.74 to 1.33; Analysis 1.3.1).

Orthopaedic surgery

Eight trials of orthopaedic surgery contributed data from 3111 participants for 30-day mortality. There was no clear effect of a restrictive compared to a liberal transfusion threshold (RR 1.16, 95% CI 0.75 to 1.79; Analysis 1.3.2).

Vascular surgery

Two trials contributed data from 157 participants for 30-day mortality. The RR for 30-day mortality was 0.98 (95% CI 0.30 to 3.25; Analysis 1.3.3).

Acute blood loss or trauma

Three trials reported mortality at 30 days among 1522 participants with acute blood loss or trauma (GI bleeding). Mortality was significantly lower when a restrictive strategy rather than a liberal strategy was used (RR 0.65, 95% CI 0.43 to 0.97; Analysis 1.3.4).

Critical care

Nine trials including 3529 participants receiving critical care for heterogeneous reasons contributed data for this outcome. The RR showed no clear effect of a restrictive compared to a liberal transfusion strategy (RR 1.06, 95% CI 0.85 to 1.32; 9 trials, 3529 participants; I^2 = 55%; Analysis 1.3.5).

Acute myocardial infarction

Three trials provided data from 820 participants with acute myocardial infarction and evaluated mortality; for this subgroup, mortality risk was higher in the restrictive strategy group than in the liberal strategy group (RR 1.61, 95% CI 0.38 to 6.88, Analysis 1.3.6). We carried out a post hoc subgroup analysis that compared 30-day mortality for acute myocardial infarction participants versus all other participants but found no differences. The P value for subgroup differences was 0.50 (Chi^2 = 0.45, df = 1; I^2 = 0%; Analysis 1.4). Although we observed a moderately elevated RR for myocardial infarction participants (RR 1.61), the three included trials were modest in size, and hence, the pooled 95% confidence interval is very wide.

Haematological malignancies

Two small trials provided data on 30-day mortality among 149 participants. The 95% confidence interval was very wide, and no conclusions can be drawn for this subgroup (RR 0.37, 95% CI 0.07 to 1.95; 2 trials, 149 participants; I^2 = 0%; Analysis 1.3.7).

Mortality by cardiac surgery, vascular surgery, myocardial infarction, and all others

We examined 30-day mortality and stratified it by the clinical context used in trials in a grouping comparing cardiac surgery, vascular surgery, myocardial infarction, and a group combining all other included trials. The overall RR for 30-day mortality stratified by clinical specialty was (to repeat findings above) 0.99 (95% CI 0.86 to 1.14; 31 trials, 16,729 participants; Analysis 1.3). Again there were no differences in 30-day mortality (test for subgroup differences: Chi^2 = 0.43, df = 3 (P = 0.93), I^2 = 0%; Analysis 1.5).

Subgroup analysis of 30-day mortality: prospectively registered versus unregistered trials or trials for which registration was post hoc

We stratified 30-day mortality according to whether or not trials were prospectively registered. Of the 31 trials that contributed data to our primary outcome, 18 (with 12,932 participants) were prospectively registered. The RR for 30-day mortality provided by pooling data from these trials was 1.08 (95% CI 0.89 to 1.31). Pooling of the 13 unregistered trials (3797 participants) led to a RR of 0.81 (95% CI 0.66 to 1.00). The test for subgroup differences indicated a difference between subgroups: Chi^2 = 4.06, df = 1 (P = 0.04), I^2 = 75.4%; Analysis 2.1), but in neither group was there a clear effect for either transfusion strategy.

Sensitivity analysis

There were no differences in 30-day mortality between trials with low versus unclear or high risk of bias in one bias domain (i.e. allocation concealment) (Analysis 3.1). The RR was 1.01 (95% CI 0.87 to 1.18) in trials with low risk of bias for allocation concealment and 0.84 (95% CI 0.51 to 1.39) for trials with unclear or high risk of bias for allocation concealment. Testing for subgroup differences yielded the following: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 = 0%.

Secondary outcomes

As detailed below, none of the other analyses on mortality or morbidity showed differences between the groups compared.

Mortality at other time intervals

We analysed mortality at hospital discharge (15 trials; 6597 participants; Analysis 4.1), at 90 days (7 trials, 4143 participants; Analysis 4.2), and at six months or longer (2 trials, 4702 participants; Analysis 4.3).

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There were no differences in mortality between transfusion strategies at hospital discharge (RR 0.86, 95% CI 0.72 to 1.03; Chi^2 = 15.36, df = 13 (P = 0.29); I^2 = 15%), but the 90-day mortality was higher for the restrictive strategy (RR 1.13, 95% CI 1.02 to 1.25; Chi^2 = 5.28, df = 6; P = 0.41; I^2 = 0%).

The two largest included trials (Carson 2011; Mazer 2017), reported mortality at six months or beyond in separate publications (Carson 2015; Mazer 2018). Results suggest no clear differences (RR 0.98, 95% CI 0.79 to 1.22; P = 0.84; Analysis 4.3). Both trials employed similar transfusion strategies.

The results of mortality analyses at hospital discharge, at 30 days, and at six months are consistent. The results of mortality analyses at 90 days were gathered from a smaller number of participants and are dominated by two particular trials (Bergamin 2017; Holst 2014), limiting interpretation.

Complex analysis in Hoff 2011 had the main purpose of defining a role for the drug nimorazole in patients receiving radiotherapy with head and neck squamous cell carcinoma (HNSCC); additional randomisation steps addressed the value of transfusion in participants who had low haemoglobin levels preradiation. This analysis combined data from a trial comparing the drug with placebo and from another comparing drug delivery at different intervals. We could not incorporate five-year mortality data within our meta-analysis, but investigators found that although transfusion improved haemoglobin levels before and during radiation treatment, it did not improve other outcomes for patients and may have had a negative impact on survival.

Clinical outcomes

We noted no differences in any groups compared for any of the clinical outcomes.

Cardiac events

Eleven trials reported data on post-enrolment cardiac events in 5577 participants. Risks of cardiac events (myocardial infarction, cardiac arrhythmias, cardiac arrest, pulmonary oedema, and angina) were not increased by the use of restrictive transfusion strategies (RR 1.03, 95% CI 0.80 to 1.32; Analysis 5.1). Heterogeneity between these trials was moderate (Chi^2 = 24.09, df = 10 (P = 0.007); I^2 = 58%). It is possible that participants were counted in more than one category for this composite outcome because these disorders are clinically inter-related (e.g. a participant could have angina that might lead to pulmonary oedema).

Myocardial infarction

Twenty-three trials reported data for myocardial infarction (fatal and non-fatal) for 14,730 participants after random allocation to liberal or restrictive transfusion arms. There was no difference between restrictive and liberal transfusion strategies (RR 1.04, 95% CI 0.87 to 1.24; Analysis 5.2). We found no evidence of heterogeneity between trials (Chi^2 = 18.63, df = 21; P = 0.61; I^2 = 0%).

Congestive heart failure

Sixteen trials reported data for congestive heart failure in 7247 participants. There was no difference between restrictive and liberal transfusion strategies (RR 0.83, 95% CI 0.53 to 1.29; Analysis 5.3). Heterogeneity between trials was moderate (Chi^2 = 22.06, df = 13; P = 0.05; I^2 = 41%).

Cerebrovascular accident: stroke

Nineteen trials reported data for stroke in 13,985 participants. There was no difference between restrictive and liberal transfusion strategies (RR 0.84, 95% CI 0.64 to 1.09; Analysis 5.4). Heterogeneity between trials was not important (Chi^2 = 12.80, df = 18; P = 0.80; I^2 = 0%).

Rebleeding

Eight trials reported data for rebleeding in 3412 participants. There was no difference between restrictive and liberal transfusion strategies (RR 0.80, 95% CI 0.59 to 1.09; Analysis 5.5). Heterogeneity between trials was not important (Chi^2 = 12.24, df = 7; P = 0.09; I^2 = 43%).

Sepsis/bacteraemia

Nine trials reported data for sepsis/bacteraemia in 4352 participants. There was no difference between restrictive and liberal transfusion strategies (RR 1.06, 95% CI 0.86 to 1.30; Analysis 5.6). Heterogeneity between these trials was not important (Chi^2 = 8.56, df = 7; P = 0.29; I^2 = 18%).

Pneumonia

Sixteen trials reported data for pneumonia in 6666 participants. There was no difference between restrictive and liberal transfusion strategies (RR 0.97, 95% CI 0.84 to 1.13; Analysis 5.7). Heterogeneity between these trials was not important (Chi^2 = 11.48, df = 15; P = 0.72; I^2 = 0.0%).

Infection

Twenty-five trials including 17,104 participants reported data for all infections defined as sepsis/bacteraemia, pneumonia, and wound infection. There was no difference between restrictive and liberal transfusion strategies (RR 0.97, 95% CI 0.88 to 1.07; Analysis 5.8). Heterogeneity between these trials was not important (Chi^2 = 21.42, df = 14; P = 0.09; I^2 = 35%).

Thromboembolism

Thirteen trials reported data for thromboembolism for 4201 participants. We calculated the odds ratio using the Peto method because the risk of thromboembolism was less than 1%. There was no difference between restrictive and liberal transfusion strategies (Peto odds ratio 1.11, 95% CI 0.65 to 1.88; Analysis 5.9). Heterogeneity between these trials was not important (Chi^2 = 14.48, df = 11; P = 0.21; I^2 = 24%).

Renal failure

Fifteen trials reported data on renal failure in 12,531 participants. There was no difference between restrictive and liberal transfusion strategies (RR 1.03, 95% CI 0.92 to 1.16; Analysis 5.10). Heterogeneity between these trials was not important (Chi^2 = 12.77, df = 14; P = 0.55%; I^2 = 0%).

Mental confusion

Nine trials reported data for mental confusion in 6442 participants. There was no difference between restrictive and liberal transfusion strategies (RR 1.11, 95% CI 0.88 to 1.40; Analysis 5.11). Heterogeneity between these trials was not important (Chi^2 = 10.29, df = 8; P = 0.24; I^2 = 22%).

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Functional recovery and fatigue

In total, 24 trials reported results showing differing scores for functional and mental outcomes and fatigue (Bracey 1999; Carson 1998; Carson 2011; de Almeida 2015; DeZern 2016; Fan 2014; Foss 2009; Gillies 2020; Gobatto 2019; Gregersen 2015; Hajjar 2010; Jairath 2015; Jansen 2020; Koch 2017; Lotke 1999; Murphy 2015; Nielsen 2014; Parker 2013; Prick 2014; So-Osman 2013; Stanworth 2020; Tay 2020; Walsh 2013; Yakymenko 2018). However, there was considerable heterogeneity in the methods and questionnaires used, and in the timing of assessments, which precluded meta-analysis. No larger trials reported significant differences in trial-specific functional or mental outcomes, or fatigue. Exploratory findings for quality of life measures from two trials in a haematological setting showed possible beneficial effects of liberal transfusion, but these results need to be evaluated in larger trials (Stanworth 2020; Yakymenko 2018). Three trials reported functional outcomes for orthopaedic surgery participants, but assessment of these functional measures in different ways precluded pooling in a meta-analysis.

Other outcomes - blood transfusions and haemoglobin

Results for transfusion and haemoglobin data were presented across the included trials, and provide key information about the implementation of transfusion protocols in trials. We anticipated high levels of heterogeneity in the analysis of transfusion outcomes, for several reasons. In particular, standard 'control' rates of transfusion practice are highly variable across the clinical specialties in which trials were identified for this update. These differing policies regarding rates of transfusion reflect practice defined in specialty guidelines and recommendations. It is usually recommended that pooled estimates are not presented when heterogeneity is so high. However, we present the pooled results here, as there was consistency regarding the direction of effect; further justification for this is provided in the Discussion.

Proportion of participants transfused

This analysis demonstrates differences in the proportions of participants transfused with RBCs in the liberal and restrictive trial arms. Data on the proportions of transfused participants were available from 42 trials (20,057 participants). The implementation of a restrictive transfusion trigger across all trials reduced the relative risk of receiving at least one RBC transfusion by 41% (RR 0.59, 95% CI 0.53 to 0.66; Analysis 6.1). Heterogeneity between these trials was substantial (Chi^2 = 1104.24, df = 41 (P < 0.00001); I^2 = 96%); however, there was consistency in the direction of the effect.

The proportions of participants transfused in liberal and restrictive trial arms were very different across different clinical contexts (Analysis 6.2); differences between subgroups were manifest (Chi^2 = 25.33, df = 6 (P = 0.0003); I^2 = 76.3%). There was a tendency for great variation within subgroups also (e.g. in the subgroup of critical care trials, heterogeneity was high (I^2 = 92%)). The acute blood loss/trauma subgroup included diverse underlying illnesses for haemorrhage, including comorbidities, leading to an I^2 of 96%. For example, Prick 2014 recruited young (otherwise healthy) women with postpartum haemorrhage, and Jairath 2015 enrolled older participants with gastrointestinal bleeding, characterised by many comorbidities. Prick 2014 contributed to a large extent to the high heterogeneity in this subgroup, and temporarily removing it from the analysis reduced heterogeneity to 77%. By contrast, participants enrolled in the subgroup of cardiac surgery trials demonstrated less variability in risk of transfusion across trials, and in this subgroup, we observed no important heterogeneity. This sensitivity analysis, although post hoc, highlights how transfusion policies in this setting differed from adult protocols in a critical care setting.

When the difference in haemoglobin thresholds between restrictive and liberal arms was 2.0 g/dL or more, the RR of transfusion was 0.57 (95% CI 0.50 to 0.64; Analysis 6.3.1), which means there was a reduction in transfusion of 43% in the restrictive arm compared to the liberal arm. When the difference in haemoglobin transfusion thresholds between restrictive and liberal transfusion arms was less than 2.0 g/dL, the RR was 0.80 (95% CI 0.63 to 1.02; Analysis 6.3.2), which means there was a reduction in transfusion of 20% (test for subgroup differences: Chi^2 = 6.11, df = 1 (P = 0.01), I^2 = 83.6%).

There was no clear difference in the proportions of participants transfused between the 17 studies (11,919 partipants) that used a restrictive strategy of 7.5 g/dL or less as a threshold (RR 0.55, 95% CI 0.48 to 0.64) versus the 19 studies (6035 participants) that used a restrictive threshold of 8.0 g/dL to 9.0 g/dL (RR 0.59, 95% CI 0.48 to 0.72; test for subgroup differences: Chi^2 = 0.18, df = 1 (P = 0.67), I^2 = 0%; Analysis 6.4).

The forest plot for the proportions of participants transfused displays grouping of trials with a RR around 0.5 for receiving a transfusion in the restrictive transfusion arm (Figure 5), which is consistent with the overall observation that participants in the restrictive arm were transfused approximately half as often as those in the liberal arm. As expected, there were no trials in which participants in the restrictive arm were transfused more often than those in the liberal arm.

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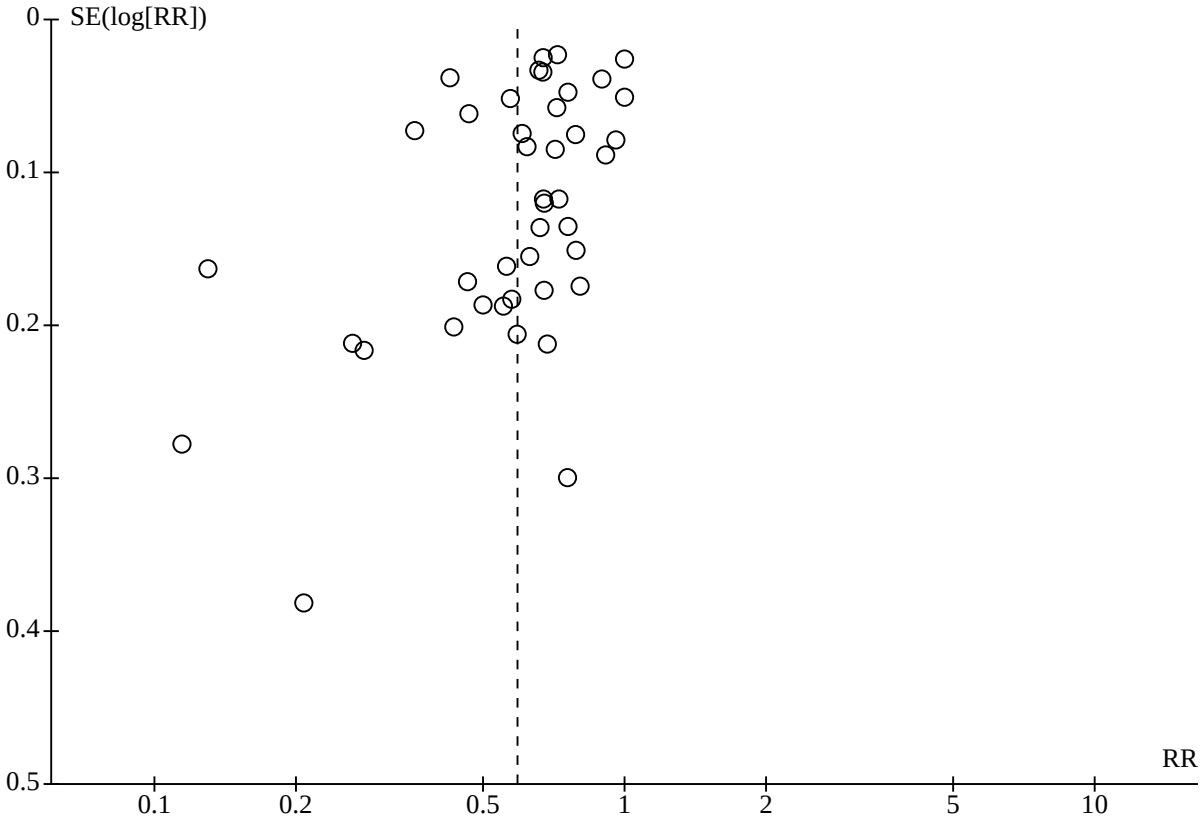
Figure 5. Funnel plot of comparison: 2 Blood transfusions, outcome: 2.1 Participants exposed to blood transfusion (all trials)



Quantity of RBCs transfused

Seventeen trials reported the quantities of blood transfused. Most trials (40) provided some information on dose of red cells, or an algorithm or a target haemoglobin for transfusion, although the level of detail varied considerably. Among the three paediatric trials, two trials indicated a range for transfusion dose of 10 mL/kg or 10 mL/kg to 15 mL/kg (Akyildiz 2018; Robitaille 2013), and one trial reported a target haemoglobin of 8.5 g/dL to 9.5 g/dL in the restrictive arm, and 11.0 g/dL to 12.0 g/dL in the liberal arm (Lacroix 2007).

Use of a restrictive transfusion trigger resulted in an average saving of 1.21 units of RBCs per transfused participant (weighted mean difference (MD) -1.21, 95% CI -1.67 to -0.75; Analysis 6.5). Heterogeneity between these trials again was substantial (Chi^2 = 1173.58, df = 16 (P < 0.00001); I^2 = 91%); however, there was consistency in the direction of the effect.

Transfusion-specific reactions

Transfusion reactions appeared to be neither well nor consistently reported, and over half (26/48) of the trials provided no information (a further two trials mentioned collecting data on such reactions but did not report them). Of the remaining 20 trials, eight reported prospectively seeking transfusion-related reactions, but found that none had occurred in either group. Twelve trials reported transfusion reactions in a heterogeneous manner that was not suited to quantitative pooling, given the variability in methods of reporting and the assigning of severity and causality assessment to transfusion.

Haemoglobin or haematocrit concentration

Nineteen trials reported the difference in haemoglobin or haematocrit levels between liberal and restrictive transfusion arms. Measures included averages (e.g. averages of different data points across a participant's stay in ICU) as well as single data points (e.g. the last measurement before discharge). When we pooled data (without regard to timing), participants assigned to a restrictive strategy had a lower haemoglobin concentration than participants assigned to a liberal transfusion strategy (mean difference -1.26, 95% CI -1.55 to -0.96; analysis not shown). Heterogeneity between these trials was substantial (Chi^2 = 914.39, df = 18 (P < 0.00001); I^2 = 98%), however, there was consistency in the direction of the effect.

Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery and in those with myocardial infarction

We analysed morbidity outcomes for a subgroup of participants with underlying cardiovascular disease, defined as those undergoing cardiac surgery or vascular surgery and those with myocardial infarction. There was no difference between restrictive and liberal transfusion strategies for myocardial infarction (RR 1.01, 95% CI 0.81 to 1.26; 8 trials, 8219 participants; Analysis 7.1); renal failure (RR 1.07, 95% CI 0.89 to1.28; 7 trials, 9198 participants; Analysis 7.2); infection (RR 1.00, 0.79 to 1.28; 8 trials, 9219 participants; Analysis 7.3); thromboembolism (RR 1.02,

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95% CI 0.11 to 9.55; 3 trials, 239 participants; Analysis 7.5); congestive heart failure (RR 0.77, 95% CI 0.24 to 2.43; 4 trials, 858 participants; Analysis 7.4); or cerebrovascular accident (RR 0.98, 95% CI 0.22 to 4.26; 4 trials, 905 participants; Analysis 7.6).

Economic and costing analyses

The protocol for this review did not include plans for formal economic analysis: findings from included trials are reported as a narrative summary only. Many trials included within this review discussed the potential cost implications of favouring a restrictive strategy or recommended cost-effectiveness analysis in future research without providing data (e.g. DeZern 2016; Lotke 1999; Stanworth 2020).

Investigators in three trials went further, making estimates based on their own data when different transfusion strategies were compared for patients with severe burns (Palmieri 2017), requiring hematopoietic cell transplantation (HCT) (Tay 2020), or with cardiac issues (Koch 2017). The former two reported that a restrictive strategy would reduce costs considerably; the latter stated only that "health care costs were similar between groups".

Of the six RCTs in which formal economic analysis was specified as an outcome, two were conducted in elective surgery (cardiac or infrainguinal) (Bush 1997; Murphy 2015). The smaller, older trial (n = 99) found a substantial difference favouring the restrictive group; the latter trial included more than 2000 participants and reported, "Total costs did not differ significantly between the groups". One trial on older, critically ill patients requiring mechanical ventilation reported increased costs for this population within the group treated with a restrictive strategy, but this was a small trial, and there was a small difference in survival outcomes (Walsh 2013).

A large trial considering outcomes of women with acute anaemia after postpartum haemorrhage concluded that intervention was more expensive per woman than non-intervention, with only a small improvement in health-related quality of life after RBC transfusion (Prick 2014).

A trial on upper GI bleeding was a feasibility trial and did report results, confirming that transfusions were an important driver of costs alongside inpatient stay and endoscopy (Campbell 2015; Jairath 2015). A large trial on myocardial infarction concluded that significant savings were likely with the use of a restrictive strategy, although a formal publication is still pending (Ducrocq 2021). For this trial, the cost-effectiveness endpoint was the incremental cost-effectiveness ratio (ICER) at 30 days. It is reported that "the restrictive strategy had an 84% probability of being cost-saving while improving clinical outcomes, i.e. "dominant" from a medico-economic standpoint" (conference proceeding; https://www.eurekalert.org/news-releases/775135).

DISCUSSION

Summary of main results

When compared with liberal transfusion strategies, restrictive transfusion strategies did not increase or decrease the risk of 30-day mortality (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.86 to 1.15; 31 trials, 16,729 participants; I^2 = 30%; moderate-quality evidence) or of any of the other outcomes assessed (i.e. myocardial infarction, stroke (high-quality evidence), thromboembolism (moderate-quality evidence), and congestive heart failure (low-quality evidence)). Restrictive transfusion strategies led to a reduction of 41% in the number of participants who received at least one unit of blood; an overall red blood cell (RBC) transfusion requirement that was approximately 1.2 units lower per participant; and a mean haemoglobin concentration that was around 1.26 g/dL lower than in liberal transfusion groups.

These findings are based on an analysis of 48 randomised controlled trials (RCTs) in this updated review that compared outcomes for participants allocated to receive transfusions of RBCs at different haemoglobin concentration thresholds. These trials enrolled 20,967 participants across diverse patient populations; most participants were adults. Since our previous 2016 review, we have included an additional 17 randomised trials.

Meta-analyses provided no evidence that restrictive transfusion policies harmed participants, or that participants benefited from the use of liberal transfusion policies, within the parameters defined in these trials. Put another way, there was no evidence of an impact on clinically important outcomes when a restrictive RBC transfusion policy rather than a liberal RBC transfusion policy was followed. Results indicate that transfusion strategy did not influence the risk of cardiovascular events, including myocardial infarction, congestive heart failure, or stroke, although statistical heterogeneity was observed in trials that evaluated congestive heart failure (P = 0.01; I^2 = 57%).

In this updated review, only three trials enrolled children and the results in paediatrics were dominated by findings from a single, large pragmatic trial (Lacroix 2007), which observed no benefit for liberal transfusion in critically ill children. Another very small randomised trial recruited only six children undergoing bone marrow transplantation and was stopped because of concerns about an excess of veno-occlusive disease in the liberal arm (Robitaille 2013); we await the results of a further ongoing trial in this setting (ISRCTN17438123; see Ongoing studies).

Subgroup analyses

With regard to our predefined clinical subgroups, results indicate that risk of death and other adverse events were not impacted by liberal or restrictive transfusion thresholds for most analyses. This is important because there are pathophysiological reasons to postulate why transfusion might impact clinical outcomes differently in different patient populations as the result of factors such as duration of anaemia (short-term transfusion dependence in critical illness versus long-term transfusion dependence in bone marrow failure) or presence or absence of an underlying restriction in cardiac function (Docherty 2016).

However, for patients with acute blood loss and for those with acute myocardial infarction, mortality may be influenced by a liberal or restrictive transfusion strategy, although the test for differences in 30-day mortality between subgroups showed no differences (P = 0.13; I^2 = 41.2%). In three trials (1522 participants) including people with gastrointestinal bleeding (included in the acute blood loss or trauma grouping), a restrictive transfusion strategy was associated with a 35% lower risk of 30-day mortality compared with a liberal transfusion strategy. The mechanism responsible for this significantly reduced risk of death may be lower risk of rebleeding under restrictive transfusion regimens (RR 0.65, 95% CI 0.43 to 0.97; Analysis 1.3.4). The reason for this effect is not known, but it may reflect higher vascular pressures following transfusion in the

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liberal transfusion group compared with the restrictive transfusion group.

Patients with acute myocardial infarction are another important patient subpopulation. In the 2016 update (Carson 2016b), two small trials included people with myocardial infarction (154 participants) for whom 30-day mortality was 3.88 times higher in the restrictive transfusion group than in the liberal transfusion group (95% CI 0.83 to 18.13). In one trial, 12.7% of participants (n = 14) undergoing cardiac catheterisation had stable coronary artery disease but did not have acute myocardial infarction (Carson 2013). These results have been extended by inclusion in the meta-analysis of Ducrocq 2021, which enrolled 666 patients and reported results for a composite major adverse cardiac events (MACE) outcome of all-cause mortality, stroke, recurrent myocardial infarction, or emergency revascularisation in 11.1% of the restrictive group and in 14.2% of the liberal group. Deaths from any cause occurred in 5.6% of the restrictive group and in 7.7% of the liberal group. With the addition of this trial, the relative risk for 30-day mortality was closer to 1.0, with wide confidence intervals (RR 1.61, 95% CI 0.38 to 6.88). A 3500-patient trial in acute myocardial infarction, called 'MINT', is currently under way and will inform this subgroup further (NCT02981407).

The nature of the restrictive transfusion intervention

Around half of the trials identified applied a restrictive threshold of 7.0 g/dL; the other half used 8.0 g/dL. The largest trial including cardiac surgery patients used a 7.5-g/dL threshold (Mazer 2017). Most participants in the 7.0 g/dL restrictive transfusion threshold trials were based in critical care and acute settings of anaemia. Clinical specialties were more varied in trials that tested an 8.0 g/dL restrictive transfusion threshold and included orthopaedic and cardiac surgery, gastrointestinal bleeding, and acute myocardial infarction. However, there was no apparent difference in risk of death at 30 days between the two strata.

We compared 30-day mortality in trials where the difference between liberal and restrictive transfusion thresholds in the trial protocol was at least 2.0 g/dL versus trials where the difference was less than 2.0 g/dL. Again, there was no evidence of a dose effect on clinical outcomes of RBC transfusion by different threshold levels of haemoglobin concentration.

Risks of infection and outcomes of recovery

In view of potential immunomodulatory effects of blood transfusion, we compared the risk of infection in three ways. We did not find evidence of an increased risk of infection associated with liberal transfusion. We combined all infections and also examined sepsis or bacteraemia and pneumonia (alone); comparative risks of infection between the two transfusion strategies were nearly identical for all of these analyses. These results varied from prior analyses in another systematic review, which reported an elevated risk of infection in the liberal transfusion group (Rohde 2014). However, they are consistent with later analyses (Carson 2016b; Carson 2018), which were based on a substantially larger number of trials.

Although 23 trials assessed functional recovery or quality of life and fatigue, these trials applied different measures or tools for assessment; therefore quantitative meta-analysis could not be supported for these outcomes.

Overall completeness and applicability of evidence

As the number of trials expands, the completeness of evidence continues to increase. Clinical trials have now evaluated many of the most common clinical specialties in which RBCs are transfused. Thus, the findings of this review are widely applicable to most clinical contexts. However, we continue to lack knowledge and sufficient precision about the safety of different transfusion thresholds for some groups of patients who frequently receive transfusion, as an insufficient number of trials with adequate power have been published for these groups. These understudied clinical contexts include people with myocardial infarction, neurological injury/traumatic brain injury, acute neurological disorder, stroke, cancer/haematological malignancy, and chronic bone marrow failure. We anticipate some of these gaps may be filled relatively soon as new trials are completed, for which details and recruitment targets are listed in Characteristics of ongoing studies.

A core rationale for RBC transfusion is to improve tissue and cellular oxygenation, but technologies for monitoring this directly, or at a cellular level, are not available routinely. Therefore, haemoglobin concentration continues to be applied as the main surrogate marker of need for transfusion in our included trials, but it may not be a reliable biomarker and it may not support a more precise or personalised approach to transfusion therapy (Baek 2019). Trials that evaluate mechanistic and physiological variables alongside haemoglobin concentration are required (Møller 2019).

Quality of the evidence

Overall, the quality of evidence across trials is good and continues to show improvement over time. The number of trials and enrolled participants has increased substantially, and the precision of the estimate of the effect of transfusion improves with updates of this review. We found relatively little heterogeneity for each clinical outcome across all analyses.

Risk of bias evaluations revealed a variety of methodological issues between trials. For more recent trials, including those reporting on larger sample sizes, evaluations of risk of bias remained generally low risk. We applied Cochrane methods for defining high or low risk of bias to all trials, but we acknowledge a number of challenges, including how to assign a single level of bias for multiple outcomes, for example, incomplete data or blinding (masking). We therefore considered risk of bias for objective (mortality) and subjective (functional and quality of life) outcomes separately. We will explore this further in future updates of this review, possibly by employing the new Cochrane 'Risk of bias 2' tool. We recognise that blinding the use of transfusion at the bedside is difficult to achieve unless trial personnel are assigned to each participant, which would be an expensive procedure. The importance of blinding will differ according to the choice of primary trial outcome; mortality is a hard endpoint (as in this review) that is less open to bias than other functional outcomes.

Outcome assessment by observers who are blind to the treatment group is probably the most rigorous practical approach for transfusion threshold trials, but this is less relevant for outcomes such as mortality. We judged the risk of bias to be high for 11 trials for subjective outcomes, including functional outcomes and quality of life. This issue of detection bias for subjective outcomes will be explored in greater detail in a further update of this review, and informed by additional trial data (see Characteristics of

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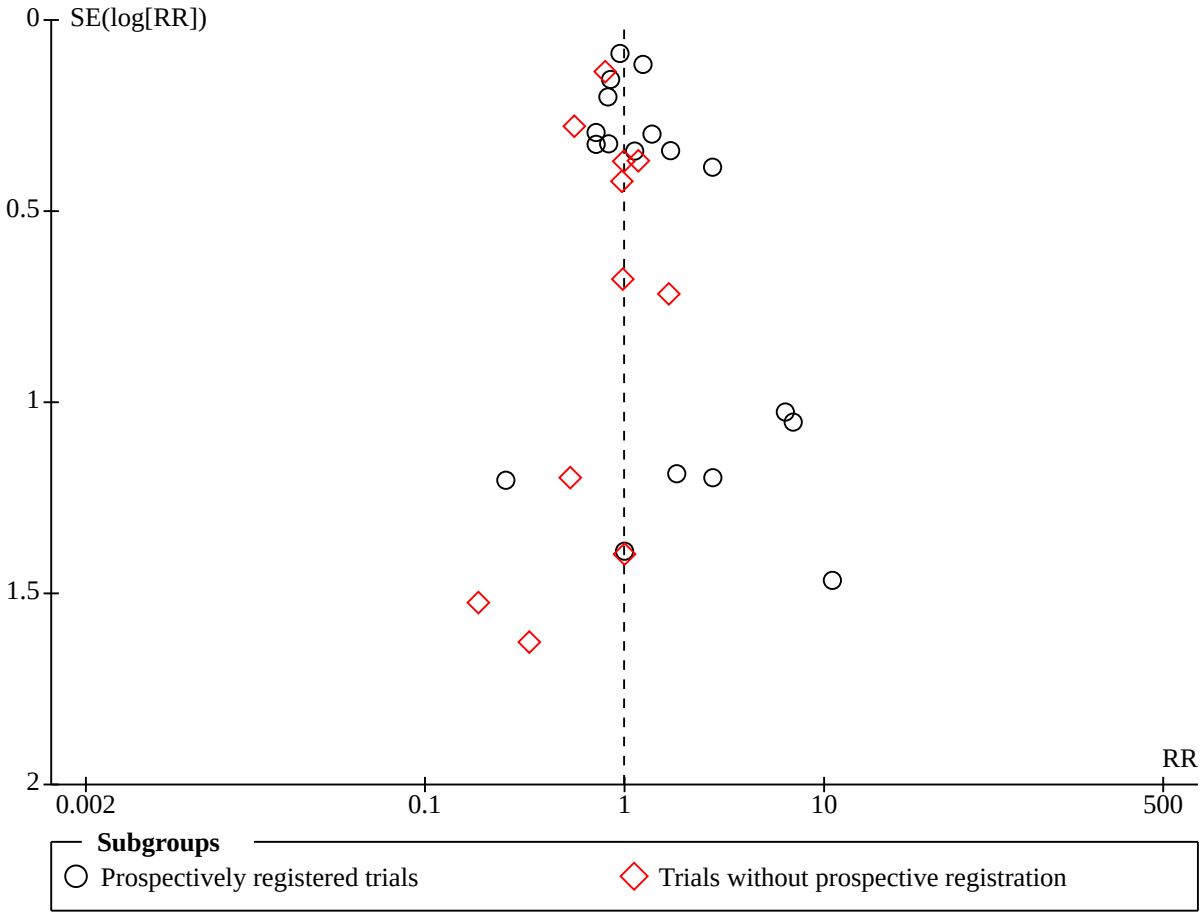
ongoing studies; Characteristics of studies awaiting classification). Maintaining the integrity of the randomisation process becomes important if the trial is not to overestimate the benefit of the intervention (Schulz 1995). We judged the risk of bias for allocation concealment - a key methodological domain - to be low for 36 trials. Only a few trials in this review did not report the methods used to conceal the allocation sequence from treating clinicians.

We recognise a number of further limitations to the quality of trial evidence, beyond those considered by the Cochrane risk of bias assessment. As described by authors of other reviews, these include variable degrees of difference in numbers of transfusions between arms, and variable degrees of actual separation of haemoglobin concentration achieved between trial arms, which often is less than defined thresholds for trial interventions stated in the protocol (Trentino 2020a; Trentino 2020b). Reasons for protocol violations, whether given as extra transfusions in the restrictive arm, or for lack of transfusions in the liberal arm, are often not reported in sufficient detail.

We considered the policy of the Cochrane Injuries Group for research integrity (Roberts 2015). We have explored possible reasons for subgroup differences between trials that were prospectively registered and those not prospectively registered ($Chi^2 = 4.06$, df = 1 (P = 0.04), $I^2 = 75.4\%$). First, we created a funnel plot and found little evidence to support selection bias (Figure 6). Second, it is possible that this statistically significant finding is a chance observation given the large number of statistical tests performed in this review. Third, we note that of the 13 trials that were not prospectively registered, seven were conducted before 2000 or 2001 when legislation regarding prospective registration was introduced in the USA and European Union, respectively, and nine of the trials were conducted before September 2007 when it was mandated by the Food and Drug Administration (FDA).

Figure 6. Funnel plot of comparison: 2 Subgroup analysis by prospective registration, outcome: 2.1 30-Day mortality



Whilst we cannot exclude the presence of selection bias, we are confident we did not miss any large trials published before 2007 that would have impacted our inferences. Indeed, the overall RR for an analysis including all trials was 0.99 (95% CI 0.86 to 1.15), while an analysis limited to the trials with prospective registration was RR 1.08 (95% CI 0.89 to 1.31).

We observed a substantial amount of statistical heterogeneity in analyses evaluating the proportions of participants transfused, the quantity of RBCs transfused, and differences in haemoglobin/haematocrit concentrations. It is conventional practice not to pool data from studies in which there is a large amount of heterogeneity, however, we chose to present pooled results

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for these transfusion outcomes for several reasons. First, the impact of restrictive transfusion on the proportion of participants transfused varied only by the magnitude of the reduction in transfusion - not the direction. In all trials, participants in the restrictive transfusion group received fewer transfusions, although the number varied because transfusion protocols were different and clinical contexts required different frequencies of transfusion. Second, we expected this heterogeneity because of the variety of contexts for clinical trials, including participant age, degrees of comorbidity, and policies for standard transfusion practice, which, in turn, reflect specialty-specific guidelines and recommendations. At one extreme, nearly all participants, if not all, with leukaemia and cancer were transfused (DeZern 2016; Stanworth 2020). Transfusion risk in participants in critical care (Hébert 1995; Hébert 1999; Lacroix 2007), or with acute blood loss (Villanueva 2013), was about 50% at the time of the trials.

In summary, we have chosen to present pooled results for outcomes of transfusion because we are evaluating the effects of restrictive transfusion practice, and because all trial estimates for changes in transfusion are consistently in the same direction. The substantial heterogeneity, therefore, reflects diversity in the strength of estimates, rather than efficacy of the policy. Reasons for diversity in the strength of trial estimates include known and expected clinical contexts and different practice guidelines used by different specialties. Subgroup explorations for transfusion outcomes reported earlier demonstrated these differences.

Potential biases in the review process

We performed extensive searches in an attempt to identify all eligible trials irrespective of publication status or language. Inspection of funnel plots did not reveal a major risk of publication bias (Figure 4; Figure 5).

Other trial limitations apply to the findings of this review. Timing of mortality reporting varied between trials, in part as a consequence of the clinical context. To address this issue, an initiative to undertake an individual patient data analysis has been commenced, including contact with all trial investigators to explore willingness to share trial data.

Randomised trials in this review may not have evaluated important clinical outcomes adequately that are specifically relevant to the use of RBC transfusions, such as quality of life. The identified trials evaluated the effects of transfusion only in hospitalised patients, and only two small trials have tested different thresholds in an outpatient population (Jansen 2020; Stanworth 2020), for whom function and fatigue would be more important endpoints.

Different grades of severity of cardiovascular events, such as myocardial infarction, congestive heart failure, or stroke, and different risks of overall infection will occur in patients; these events may present in ways that are not always clinically overt and so are more subjective in interpretation. This is important because RBC transfusions may have both harmful and beneficial effects on the risk of these outcomes, for example, balancing prothrombotic tendencies against protective mechanisms to limit restrictions in myocardial oxygen delivery. Future trials need to establish robust definitions of all outcomes (Docherty 2016). Despite the large number of participants included in these trials, there remains inadequate power for many outcomes.

Agreements and disagreements with other studies or reviews

The results of this review are consistent with previous published systematic reviews and guidance documents (Carson 2012a; Docherty 2016; Holst 2015; Meybohm 2020). A review of reviews reported no evidence that a difference in mortality exists between patients assigned to a restrictive or a liberal transfusion strategy (Trentino 2020a). These overall findings provide no evidence that restrictive transfusion policies harm patients within the limits defined by the trials.

Multiple reviews have addressed outcomes in selected subgroups or subpopulations of patients. A review by Fominskiy aimed to assess effects of liberal and restrictive RBC transfusion strategies on mortality in perioperative and critically ill adult patients through a meta-analysis of relevant trials (Fominskiy 2015); a more recent review focused on cardiac surgery (Shehata 2019). A meta-analysis of trials in gastrointestinal bleeding reported evidence of harm with application of liberal thresholds in this patient group (Odutayo 2017), as found in our review, although our review has identified one further trial in gastrointestinal bleeding (Kola 2020). We suggest some caution in interpretation of systematic reviews that report only separate subpopulations of the wider trial literature. Anaemia is the common presenting clinical problem for all patients when a red cell transfusion is considered, irrespective of clinical setting. There is a risk that the patterns of findings in different clinical contexts are inappropriately selective to a small subpopulation. The clinical decision process for transfusion in one clinical context may need to draw on findings of safety as reported across all randomised trials in different clinical settings, for a common intervention of RBC.

The results of our meta-analyses need to be viewed against studies or reviews of large observational studies that have reported comparisons of clinical outcomes at varying haemoglobin levels in transfused and non-transfused patients. Publications of the observational literature have reported findings at variance with the randomised trial literature (Carson 1998; Hébert 1997; Hébert 1999; Patel 2015; Spiess 1998; Wu 2001; Wu 2007; Wu 2010). Reviews of observational data have reported an increase in risk of death associated with transfusion (Chatterjee 2013; Marik 2008). However, a limitation of observational studies is that there may be residual confounding by indication, despite extensive statistical adjustment of the results. It is possible that differences in patient characteristics between those who were transfused and those who were not transfused may not have been identified or adjusted for adequately. In contrast, results of the meta-analysis of clinical trials performed in this review update show no increase in risk of death for liberal transfusion thresholds compared with restrictive transfusion thresholds. Despite assertions to the contrary (Benson 2000; Concato 2000), we continue to believe there is a need for adequately powered, rigorously performed, randomised trials to provide the highest level of evidence when effects of different transfusion policies are tested, as the way of overcoming these limitations.

The transfusion policies reviewed here represent fairly small but significant modifications to routine clinical practice. They are consistent with the recommendations of published clinical practice guidelines (AAGBI 2008; ASA 2006; BCTMAG 2003; Carson 2012a; Carson 2016b; Mueller 2019; Napolitano 2009; NBUGI 2001; Retter 2013; STSBCGTF 2011). Transfusion triggers (in terms of

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haemoglobin levels) were most often in the range of 7.0 g/dL to 10.0 g/dL. In fact, the 'restrictive' transfusion triggers in some trials were equivalent to the 'liberal' triggers used in other trials. Nevertheless, trials documented significant reduction in exposure of patients to unnecessary RBC transfusion. Our findings for red cell transfusion strategies should be interpreted alongside findings for the use of 'alternative' agents to red cells or blood-sparing techniques, such as intravenous iron (Richards 2020), cell salvage/blood conservation (Carless 2010a; STSBCGTF 2011), and antifibrinolytic drugs (Henry 2011). Adoption of a conservative transfusion threshold appears to be as effective, if not more effective, in the context of Patient Blood Managment implementation, and is likely to cost less (Roman 2020).

Some guidelines have recommended RBC transfusion for symptoms or haemodynamic instability, rather than for a specific trigger haemoglobin level (AAGBI 2008; ASA 2006; Napolitano 2009; NBUGI 2001). Three studies tested this approach to transfusion: a pilot study involving 84 participants (Carson 1998), a trial involving 2016 participants (Carson 2011), and a 110-participant trial for acute myocardial infarction (Carson 2013), in which patients could be transfused if they exhibited symptoms or had a haemoglobin concentration less than 8.0 g/dL. These studies found no differences in functional recovery, mortality, or morbidity among patients in the restrictive (symptomatic) transfusion group in orthopaedic surgery trials (Carson 1998; Carson 2011), although in the trial involving patients with acute myocardial infarction (Carson 2013), there was a tendency towards worse outcomes in the restrictive transfusion group.

AUTHORS' CONCLUSIONS

Implications for practice

Analysis of published evidence reveals that transfusing at a restrictive strategy of 7.0 g/dL to 8.0 g/dL, compared with a liberal haemoglobin threshold of 9.0 g/dL to 10.0 g/dL, across a broad range of hospitalised patients does not have an adverse effect on clinical outcomes, including 30-day mortality, myocardial infarction, congestive heart failure, and infection.

Given there is no evidence of additional benefit of red blood cell (RBC) transfusion at higher haemoglobin concentration thresholds (9.0 g/dL to 10.0 g/dL), and that blood for transfusion is a costly and scarce biological resource with finite risks, a restrictive transfusion trigger policy (7.0 g/dL to 8.0 g/dL) could be widely adopted. A restrictive transfusion policy is not associated with increased adverse events and reduces both risk of exposure to RBC transfusion and the total number of units transfused.

Trial interventions varied on the haemoglobin concentration used to define the restrictive transfusion group. About half of the trials used a 7.0-g/dL threshold, and the other half used a threshold of 8.0 g/dL to 9.0 g/dL. However, within each clinical subgroup, the number of clinical trials (and the total numbers of enrolled patients) testing restrictive thresholds at 7.0 g/dL varied. The exact implications for transfusion practice regarding the nature of restrictive haemoglobin thresholds will, therefore, vary by clinical group.

In critical care trials, a 7.0-g/dL threshold was used most frequently and shown to have a similar safety profile to higher thresholds for mortality (RR 1.06, 95% CI 0.85 to 1.32). Similarly, a restrictive threshold of 7.0 g/dL was used in trials including patients with acute blood loss from gastrointestinal bleeding; evidence indicates that these patients have lower risk of 30-day mortality with restrictive transfusion that uses a 7.0-g/dL threshold.

In patients undergoing cardiac surgery, a restrictive threshold of 7.5 g/dL (rather than 7.0 g/dL) was used in the largest trials and shown to have a risk for mortality which was similar to that of higher thresholds.

In trials of orthopaedic surgery, the restrictive strategy used most frequently was 8.0 g/dL, which had a similar risk profile for mortality as higher transfusion thresholds. In this clinical subgroup, it is not possible to conclude that 7.0 g/dL is as efficacious as 8.0 g/dL, without testing lower thresholds in trials.

In other clinical subgroups, the results do not provide adequate evidence to conclude which specific restrictive transfusion threshold should be applied. These subgroups include vascular surgery and haematological malignancies, where trials are insufficient in number or recruit only small numbers of participants.

The analysis does provide some evidence that a restrictive strategy might be appropriate for patients with underlying cardiovascular disease. The REALITY trial conducted in patients with acute myocardial infarction found fewer deaths and fewer major adverse cardiac events (MACE) with a restrictive threshold of 8.0 g/dL (Ducrocq 2021). However, pooled analysis of all three trials in people with acute myocardial infarction (820 participants) reveals that the risk ratio of 1.61 and very wide 95% confidence intervals (0.38 to 6.88) are also consistent with the possibility of significant benefit for more liberal transfusion policies.

In summary, it is not possible to suggest a single restrictive transfusion threshold across all clinical groups and patients with anaemia. While it is possible that a 7.0-g/dL threshold could be used in most adult patients, in some settings trial data for thresholds of 7.0 g/dL do not exist. Without these data, it is impossible to be certain of the effects of higher or lower thresholds in these settings. Trials that should clarify the optimal threshold in some of the most important subgroups that currently lack data are now underway (Ongoing studies).

Evidence is insufficient to evaluate the effects of different strategies on functional recovery. Quality of life is an important outcome in many trial settings, for example, people who are transfusion dependent and are managed in outpatient settings. In our review, most included randomised trials were based on patients hospitalised for the management of 'acute' anaemia. In contrast, patients with chronic bone marrow failure, such as myelodysplasia, are transfusion dependent for prolonged periods of time at home, and this may persist for years, yet our understanding of the impact of different transfusion policies on quality of life and functional outcomes for these patients is incomplete.

For countries where there are concerns about microbiological screening and the safety of donated blood, the data in this updated review constitute a strong basis for avoiding liberal RBC transfusion in many clinical settings. The benefits of minimising allogeneic RBC transfusion are likely to be greatest when there is doubt about the safety of the blood supply (WHO 2016). There is a need for practice and research to implement our review findings, with support for education and training and updating of robustly

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constructed guidelines (Kwan 2020; Pavenski 2018; Smith 2020; Vlaar 2020).

Implications for research

The totality of research evidence now allows us to make firmer recommendations for research priorities. Further randomised trials should be targeted to address specific research questions when the strength of evidence-based recommendations has significant uncertainty, rather than repeating trials in clinical settings or at haemoglobin thresholds for which the evidence base is better defined. Acute cardiovascular disease is a high-priority area, for which a restrictive approach may not be as safe, but ongoing larger trials have the potential to provide additional evidence (NCT02981407; Shah 2020). Limited data are available for participants in clinical contexts of acute coronary syndrome, myocardial infarction, neurological injury/traumatic brain injury, acute neurological disorders, and stroke. Areas of uncertainty in cancer and haematological malignancy include chronic bone marrow failure and the role of transfusion at different thresholds for patients receiving radiotherapy (Hoff 2011). Liberal thresholds for red cell transfusion could provide important additive benefits for important outcomes such as fatigue and quality of life for elderly patients with chronic bone marrow failure, who may be transfusion dependent for many years (Stanworth 2020).

Although one large pragmatic trial has been undertaken in critically ill children (Lacroix 2007), many children with anaemia, although eligible, were not recruited into this trial, and further research is warranted to examine the generalisability of these trial findings for all groups of sick infants and children, including those with cardiac disorders. Patients with severe burn injuries who require large volumes of red cells may also present in a clinical context that requires further research.

In summary, we believe that in these selected clinical contexts, clinical goals and pathophysiology preclude generalisation from the completed trials included in this review to date, and there remains uncertainty regarding optimal transfusion practices in these subgroups.

There is a need to continue to update this review, given the large number of ongoing trials, which reflects an active programme of research in the field of red cell transfusion research. All new trials should be adequately powered and apply consistent definitions for clinical outcomes, such as infection, myocardial infarction and ischaemic heart disease (Docherty 2018). Outcomes of importance in trials will continue to include mortality, along with outcomes that are more specific and relevant to the clinical setting, such as function and quality of life measures and bleeding endpoints in transfusion-dependent patients with cancer and haematological malignancy. All new trials should be prospectively registered, to assist researchers in assessing risk of selective outcome reporting and other matters related to research integrity.

Trials are also needed to evaluate haemoglobin concentrations below 7.0 g/dL, such as 6.0 g/dL (Yao 2020), which may be especially relevant in countries with suboptimal blood safety and inadequate blood supply (Maitland 2019). One randomised feasibility trial identified as ongoing in children undergoing allogeneic haematopoietic stem cell transplantation is comparing restrictive versus liberal red cell transfusion strategies using haemoglobin concentrations of < 6.5 g/dL and < 8.0 g/dL respectively (ISRCTN17438123). Further research should recognise the need for gender-specific reference ranges for haemoglobin concentration (Butcher 2017).

A limitation of this trial-level meta-analysis is the difficulty in analysing subgroups of patients with varying underlying diseases, age, and clinical settings. This is especially important when considering transfusion thresholds because there are pathophysiological and clinical data to suggest that the optimal transfusion threshold could differ according to the patient's underlying co-morbidity (e.g. cardiovascular disease), gender and age. One approach to address this limitation would be to conduct individual patient data meta-analysis by obtaining and analysing detailed information on each patient enrolled in the trials.

Research is needed to identify methods used to measure oxygen delivery to vital organs directly, and to define the need for red cell transfusion more precisely. This recognises the challenge of applying haemoglobin concentration as an imperfect surrogate marker of transfusion requirements (Baek 2019; Mueller 2019; Ochocinska 2020). Although it is beyond the scope of this review, further research should explore factors related to the red cell product used for transfusion, including differences in processing and characteristics of the product. As one example of a donor-specific factor that may be highly relevant for interpretation of trial results, our analysis revealed that only 16 trials clearly specified use of leuco-depleted red cells in the trial protocol (Turner 2018).

Consideration should be given to aspects of trial design in the future. The most common design identified in eligible studies in our review remains the parallel two-arm trial, in which two (arguably arbitrarily defined) thresholds for haemoglobin concentration are compared. A two-arm trial design, while simple and pragmatic, may be an inefficient approach for identifying the exact optimal threshold for transfusion in a setting - it may indeed be a different threshold than those tested in the trial. We and other groups have highlighted the fact that the actual separation of haemoglobin concentrations attained in trials varies considerably (Trentino 2020a; Trentino 2020b), and this separation rarely approaches the hoped for differences defined by protocol trial interventions.

Allied research is needed to address the optimal target haemoglobin concentration post transfusion, which will depend on the dose of transfusion given. Doses of red cells in adults are increasingly recommended as single-unit transfusions in non-bleeding patients, but the evidence base is limited (Shih 2018). The question of optimal dose for transfusion is particularly relevant for children and infants, given that a common paediatric dose is 10 mL/kg to 15 mL/kg, which is much greater proportionately by weight than the single unit dose (or bag) commonly used in adults (New 2016).

Ultimately, the optimal threshold for transfusion is likely to vary between patients, and new trial designs are needed that can test and evaluate targeted or personalised approaches to the need for transfusion, possibly incorporating individual physiological parameters. Indeed, it has been argued that current trials do not allow a genuine 'standard of care' arm (Wang 2010), which would mirror current clinical practice by clinicians at the bedside.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akyildiz 2018

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site, non-inferiority, 'per-protocol' approach **Setting:** PICU, tertiary (university-affiliated hospital), Kayseri, Turkey **Recruitment:** January 2014 to December 2015 **Maximum follow-up:** in-hospital stay
Participants	180 children in paediatric ICU randomised; 160 completed follow-up • Liberal group: n = 89; M/F 41/48; median (IQR) age = 36 (24 to 48) months • Restrictive group: n = 71; M/F 36/35; median (IQR) age = 72 (36 to 84) months
Interventions	• Liberal group: Hb < 10 g/dL trigger • Restrictive group: Hb < 7 g/dL trigger
Outcomes	**Primary outcomes:** cardiac output and other haemodynamic measures **Secondary outcome:** in-hospital mortality
Notes	**Trial registration:** not confirmed. Internal (university) documentation: registration TSA-2014-5299 **Trial funding/Sponsor:** Erciyes University Scientific Research Unit **Conflict of interest:** study authors declare they have none

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Randomization was provided by a coin toss" (Akyildiz 2018 p 2)
Allocation concealment (selection bias)	High risk	No information was provided beyond the statement above

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Akyildiz 2018 *(Continued)*

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we will grade risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"Cardiologists who assessed the cardiac output measurements were blinded to treatment allocations" (Akyildiz 2018 p 2) No other subjective outcomes were used in this review
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a differential loss to follow-up, with more losses in the restrictive arm (1 loss in the liberal arm and 19 in the other)
Selective reporting (reporting bias)	Unclear risk	No evidence of prospective registration; trial protocol unavailable; information insufficient to make a judgement
Other bias	Low risk	None apparent

Bergamin 2017

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** ICU, tertiary (university teaching hospital), São Paulo, Brazil **Recruitment:** June 2012 to May 2014 **Maximum follow-up:** 90 days
Participants	300 participants 18 years of age or older with a diagnosis of solid cancer and septic shock in ICU • Liberal group: n = 149; M/F 70/79; mean (SD) age = 61.6 (12.9) years • Restrictive group: n = 151; M/F 84/67; mean (SD) age = 61.4 (13.5) years
Interventions	Liberal transfusion at Hb < 9 g/dL Restrictive transfusion at Hb < 7 g/dL
Outcomes	**Primary outcome:** 28-day mortality **Secondary outcomes:** need for advanced organ support (invasive mechanical ventilation, inotropic therapy, or renal replacement therapy), cerebral ischaemia (diagnosed by imaging and new focal deficit), acute myocardial infarction, mesenteric ischaemia, limb ischaemia, and serious adverse reactions (haemolytic transfusion reactions, anaphylaxis, transfusion-associated lung injury, or transfusion-associated circulatory overload) in the 28 days after randomisation; ICU and hospital length of stay; ICU re-admission; death by 60 and 90 days after randomisation
Notes	**Trial title:** Transfusion Requirements in Critically Ill Oncologic Patients (TRICOP)

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Bergamin 2017 *(Continued)*

Trial registration: NCT01648946. Study start date was June 2012. Registration first submitted 19 July 2012; posted 25 July 2012

Trial funding: not reported. Sponsor was Instituto do Cancer do Estado de São Paulo, Brasil
COI statement by investigators: "Dr. Park disclosed government work. The remaining authors have disclosed that they do not have any potential conflicts of interest" (Bergamin 2017 p 766)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly assigned to the liberal or restrictive RBC transfusion strategy by means of an Internet based system that concealed assignments" (Bergamin 2017 p 767)
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	"Two blinded investigators assessed primary and secondary outcomes by patient records review or by telephone call (long-term survival). There was no identification of transfusion strategy group on patients, patient records, or patient beds. Patients and investigators who collected outcomes had no access to transfusion data and were unaware of the group assignment" (Bergamin 2017 p 767) "Transfusion decisions were not performed blindly ... Physicians and nurses of the ICU were aware of the groups of treatment ... Patients were unaware of the group assignment" (Bergamin 2017 p 767)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up; data analysed on intention-to-treat model
Selective reporting (reporting bias)	Low risk	Outcomes as specified in the trial registration (NCT01648946) appear in full in the published paper
Other bias	Low risk	None identified

Blair 1986

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** tertiary (university teaching hospital), London, UK **Recruitment:** not specified; pre-1987

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Blair 1986 *(Continued)*

	Maximum follow-up: in-hospital stay
Participants	50 consecutive participants with severe upper GI haemorrhage were randomised to 1 of 2 groups: • Liberal group: n = 24; mean (SD) age = 64 (17.6) years • Restrictive group: n = 26; mean (SD) age = 60 (17.8) years
Interventions	• Liberal group: received at least 2 units of RBCs immediately at admission and during their first 24 hours in hospital • Restrictive group: no transfused RBCs unless Hb was < 8.0 g/dL or shock persisted after initial resuscitation with Haemaccel
Outcomes	Blood usage (units), rebleeding, mortality, clotting times, Hct on admission/discharge, kaolin cephalin clotting time after 24 hours, impedance clotting time after 24 hours
Notes	**Trial registration:** not confirmed **Trial funding:** Crawley and Jersey Research Fund (UK) **COI statement by investigators:** none provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Investigators reported no information regarding this domain
Allocation concealment (selection bias)	Unclear risk	Investigators reported no information regarding this domain
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we grade risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data (all data were collected during hospital stay)
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases identified

Bracey 1999

Study characteristics

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Bracey 1999 *(Continued)*

Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** non-profit research/treatment centre, Houston, TX, USA **Recruitment:** February to November 1997 **Maximum follow-up:** in-hospital stay
Participants	428 consecutive participants undergoing elective primary coronary artery bypass graft surgery, randomly assigned to 1 of 2 groups: • Liberal group: n = 212; M/F 82/18; mean (SD) age = 61 (11) years • Restrictive group: n = 216; M/F 83/17; mean (SD) age = 62 (11) years
Interventions	• Liberal group: received transfusions on the instructions of their individual physicians, who considered clinical assessment of the participant and institutional guidelines, which proposed a Hb < 9.0 g/dL as the postoperative threshold for RBC transfusion • Restrictive group: received an RBC transfusion in the postoperative period at Hb < 8.0 g/dL
Outcomes	Mortality, length of hospital stay, blood usage (units), blood loss, complications, infection rates, cardiac events
Notes	**Trial registration:** not confirmed **Trial funding:** not reported **COI statement by investigators:** none provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants "were randomly assigned on the basis of the last digit of their medical record number" (Bracey 1999 p 1071) Review authors' judgement: this is not a genuinely random method of allocation. High risk of bias
Allocation concealment (selection bias)	High risk	Sequence generation (record number) obviated concealment of any kind
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we grade risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Investigators provided no information regarding the survey questionnaire "When analyzed by Hb content, FACT-F and FACT-An scores were significantly different on postoperative Day 5, when patients with a Hb <9 g per dL were compared with patients with a Hb level >10 g per dL (p = 0.004). However, the same groups had similar survey scores on postoperative Day 3. Because the goal of our study was to maintain Hb content at >8 g per dL, we reanalyzed the subgroup and excluded patients with lowest Hb <8 g per dL. Then, survey

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Bracey 1999 *(Continued)*

		scores did not differ significantly between low and high Hb groups...." (Bracey 1999 p 1075)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial used intention-to-treat analysis. Mortality data were reported for all participants, but for analysis of transfusion, participants who died during hospitalisation were excluded from analysis, as "early death precludes observation of transfusion and morbidity rate" (Bracey 1999 p 1075)
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	None identified

Bush 1997

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** university teaching hospital, Sacramento CA, USA **Recruitment:** August 1995 to November 1996 **Maximum follow-up:** in-hospital stay
Participants	99 participants undergoing elective aortic or infrainguinal arterial reconstruction were randomised to 1 of 2 groups: • Liberal group: n = 49; M/F = 41/8; mean (SD) age = 64 (11) years • Restrictive group: n = 50; M/F = 32/18; mean (SD) age = 66 (10) years
Interventions	• Liberal group: had Hb maintained at or > 10.0 g/dL • Restrictive group: transfused only when Hb fell to < 9.0 g/dL
Outcomes	**Primary endpoints:** myocardial ischaemia, myocardial infarction, death during hospitalisation **Secondary endpoints:** length of ICU stay, hospital stay, graft patency
Notes	**Trial registration:** none confirmed **Trial funding:** not reported **COI statement by investigators:** none reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Sealed envelopes were chosen at random for participant assignment" (Bush 1997 p 144)
Allocation concealment (selection bias)	Low risk	Sealed envelopes were chosen at random for participant assignment

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Bush 1997 *(Continued)*

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we have graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data on subjective outcomes (e.g. function) Review authors' judgement: low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data appeared to be complete
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases identified

Carson 1998

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, international trial **Setting:** 4 university-affiliated hospitals (3 in the USA; 1 in the UK) **Recruitment:** March 1996 to March 1997 **Maximum follow-up:** 60 days
Participants	84 hip fracture participants undergoing surgical repair who had postoperative Hb < 10.0 g/dL were randomly assigned to 1 of 2 groups: • Liberal group: n = 42; M/F = 9/33; mean (SD) age = 81.3 (8.1) years • Restrictive group: n = 42; M/F = 11/31; mean (SD) age = 83.3 (10.8) years
Interventions	• Liberal group: received 1 unit of packed RBCs at the time of random assignment and as much blood as necessary to keep Hb > 10.0 g/dL • Restrictive group: received RBC transfusion for symptoms of anaemia or when Hb dropped to < 8.0 g/dL
Outcomes	Mortality, length of hospital stay, blood usage (units), complications, pneumonia, stroke, thromboembolism
Notes	**Trial registration:** not reported **Trial funding:** supported by Richard C Reynolds Chair **COI statement by investigators:** none identified
Risk of bias	

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Carson 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedules were stratified by clinical site and cardiovascular disease state. Randomisation was designed in blocks of 2 to 8 participants to avoid imbalance within a site (Carson 1998 p 524)
Allocation concealment (selection bias)	Low risk	Study personnel at clinical sites randomly assigned participants by contacting the data co-ordinating centre's 24-hour automated telephone service (Carson 1998 p 523)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	There was no blinding of participants or personnel. The primary outcome of mortality allowed a judgement of low risk of bias
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"Study nurses, blind to the transfusion status of the patient, obtained information from patients or proxies on survival, place of residence, and functional status" (Carson 1998 p 524)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 84 enrolled patients, 3 refused to comply with the study protocol after randomization, although follow-up was completed at 60 days. The assigned transfusion strategy was successfully implemented in 93.8 percent (76/81) of the remaining patients. One patient in the threshold transfusion group did not receive a transfusion, and four patients in the symptomatic transfusion group received a transfusion in violation of the protocol (i.e., they did not have symptoms of anemia or a Hb of 8 gldL). Sixty-day follow-up was obtained in all patients" (Carson 1998 p 525) Data were analysed by the intention-to-treat principle
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases identified

Carson 2011

Study characteristics	
Methods	**Design:** Randomised, unblinded, parallel 2-group, multicentre, international trial **Setting:** 47 clinical sites in the USA and Canada **Recruitment:** Juyl 2004 to February 2009 **Maximum follow-up:** up to 5 years (mean of 3.1 years)
Participants	2016 participants aged 50 years or older who were undergoing surgical repair of a hip fracture, with Hb < 10.0 g/dL within 3 days after surgery, and who had clinical evidence of cardiovascular disease (original protocol, valid until December 2005) or cardiovascular risk factors (from December 2005 onwards, following change to expand criteria to enhance recruitment) • Liberal group: n = 1007; M/F = M/F = 250/757; mean (SD) age = 81.8 (8.8) years

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Carson 2011 *(Continued)*

	• Restrictive group: n = 1009; M/F = 239/770; mean (SD) age = 81.5 (9.0) years
Interventions	• Liberal group: received packed RBCs when Hb dropped to < 10.0 g/dL • Restrictive ('symptomatic strategy') group: received transfusion if they developed symptoms of anaemia or if Hb fell to < 8.0 g/dL
Outcomes	**Primary outcomes:** inability to walk 10 feet (or across a room) without human assistance, death prior to closure of the window for 60-day mortality **Other outcomes:** Hb, ACS, in-hospital myocardial infarction, unstable angina or death, disposition on discharge, survival, functional measures, fatigue/energy, re-admission to hospital, pneumonia, wound infection, thromboembolism, stroke or transient ischaemic attack, cognition (Gruber-Baldini), mortality at 30 days Results for long-term mortality were published after the main trial report (Carson 2015)
Notes	**Trial title:** FOCUS **Trial registration:** NCT00071032. Protocol available on journal website **Trial funding:** National Heart, Lung, and Blood Institute (USA) **COI statement by investigators:** apart from participating as investigators in the trial, the paper reported, "No other potential conflict of interest relevant to this article was reported" (Carson 2011 p 1). NCT record states all PIs employed by sponsoring organisation (Rutgers)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Data co-ordinating centre staff prepared randomisation schedules for each site using randomly ordered block sizes of 2, 4, 6, or 8 (Carson 2011 p 2)
Allocation concealment (selection bias)	Low risk	The trial used an automated telephone randomisation system (Carson 2011 p 2)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	"After randomization, clinical-site staff members, clinicians, and patients were aware of study-group assignments" (Carson 2011 p 2454) "The primary and secondary outcomes were assessed blinded to treatment assignment in hospital and later, during telephone follow-up" "Nurses at the clinical coordinating center who were not involved with study implementation and were unaware of study-group assignments telephoned patients or proxies at or close to 30 days and 60 days after randomization to ascertain outcomes after hospital discharge. They spoke directly to patients who were accessible by telephone or to proxies if patients were cognitively impaired or could not talk on the telephone" (Carson 2011 p 2455)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	Functional measures, fatigue, and myocardial infarction were assessed blinded to treatment assignment. Other in-hospital morbidity (i.e. pneumonia) was assessed by clinical staff with knowledge of assignment "Nurses at the clinical coordinating center who were not involved with study implementation and were unaware of study-group assignments tele- phoned patients or proxies at or close to 30 days and 60 days after randomization to

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Carson 2011 *(Continued)*

		ascertain outcomes after hospital discharge. They spoke directly to patients who were accessible by telephone or to proxies if patients were cognitively impaired or could not talk on the telephone" (Carson 2011 p 2455)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for primary outcomes and most secondary outcomes were nearly complete: "there were 14 withdrawals, 2 losses to follow-up, and 1 incomplete follow-up ascertainment; follow-up for the primary analysis was obtained in 99.2% of the patients. Of the 1999 patients included in the primary analysis, we directly interviewed 1075 (53.8%) and obtained data on 923 (46.2%) by proxy; the source of information was missing for 1 patient" (Carson 2011 p 5)
Selective reporting (reporting bias)	Low risk	Reporting was complete (ascertainable by comparison of publications with trial registration and protocol)
Other bias	Low risk	No other biases identified. It is noted that there was a change to inclusion criteria and a reduction in the recruitment target. In the follow-up trial of long-term outcomes for mortality, 10% of cases could not be linked to death registries

Carson 2013

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre pilot trial **Setting:** 8 US hospitals **Recruitment:** March 2010 to May 2012 **Maximum follow-up:** 6 months
Participants	Participants with acute myocardial infarction or undergoing cardiac catheterisation with Hb < 10 g/dL • Liberal group: n = 55; M/F = 28/27; mean (SD) age = 67.3 (13.6) years • Restrictive group: n = 55; M/F = 27/28; mean (SD) age = 74.3 (11.1) years
Interventions	• Liberal group: received 1 unit of RBCs following randomisation and enough blood to maintain Hb > 10 g/dL • Restrictive group: received transfusion if participants developed symptoms of anaemia or if Hb fell to < 8 g/dL
Outcomes	**Primary outcomes:** death, myocardial infarction, unscheduled revascularisation **Secondary outcomes:** 30-day and 6-month mortality, long-term mortality, myocardial infarction, congestive heart failure, stroke, thromboembolism, pneumonia
Notes	Intention was to recruit 200 participants; the Data Safety Monitoring Committee approved early termination of recruitment at 110 participants 12.7% of patients had stable coronary artery disease, were undergoing a cardiac catheterisation, and did not have acute myocardial infarction **Trial registration:** NCT01167582 **Trial funding:** National Heart, Lung, and Blood Institute **COI statement by investigators:** COI statement not made available in publication

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Carson 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer programme generated allocation sequence, implementing a permuted block randomisation process stratified by clinical site and clinical diagnosis
Allocation concealment (selection bias)	Low risk	Trial used an automated, centralised telephone system for allocation
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' "We were unable to blind the treating physician or patient to the transfusion strategy. However, we did classify outcomes blinded to treatment assignment. We do not know if process of care differed between the two groups of patients although adherence to the protocol was similar"
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "Outcome adjudications and even Sample t classifications were performed by a committee composed of two cardiologists or infectious disease specialist (for infections) masked to the assignment group. Disagreements were settled by consensus" "We contacted all surviving patients discharged from the hospital by telephone at 30 days and 6 months after randomization to learn of their vital status and repeated hospital admissions. Follow-up telephone calls were performed centrally by the Clinical Coordinating Center. If a patient was admitted to the hospital, copies of medical records were obtained"
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function) All outcomes adjudicated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 of 110 participants was lost to follow-up
Selective reporting (reporting bias)	Low risk	**Trial registration:** NCT01167582. Feasibility study: all clinical outcomes were reported
Other bias	Low risk	Intention was to recruit 200; the Data Safety Monitoring Committee approved early termination of recruitment at 110 participants. We assess this as low risk of bias given the independence of the Committee

Cooper 2011

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, 2-site trial **Setting:** 2 VA hospital centres, DC/Virginia, USA **Recruitment:** May 2003 to October 2009

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Cooper 2011 *(Continued)*

	Maximum follow-up: 30 days
Participants	45 participants with acute myocardial infarction and Hct < 30% • Liberal: n = 21; mean (SD) age = 76.4 (13.5) years • Restrictive: n = 24; mean (SD) age = 70.3 (14.3) years
Interventions	• Liberal group: transfusion occurred when Hct < 30% to maintain it between 30% and 33% • Restrictive group: transfusion occurred when Hct < 24% to maintain it between 24% and 27%
Outcomes	**Primary clinical safety measurements:** in-hospital death, recurrent myocardial infarction, new or worsening congestive heart failure
Notes	**Trial registration (prospective):** NCT00126334 **Trial funding:** the trial was supported by the Cardiovascular Research Institute of the Washington Hospital Center and received no external funding **COI statement by investigators:** COI statement not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned in a 1:1 ratio to 1 of 2 treatment groups by the coordinating center using consecutively numbered opaque envelopes" (Cooper 2011 p 1108)
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	"Patients were followed daily by study personnel during their hospitalization and contacted by telephone at 30 days from randomization. Events were determined by the local study investigator" (Cooper 2011 p 1108) Howver, blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	In-hospital follow-up was complete; 3 of 45 participants were lost to follow-up at 30 days
Selective reporting (reporting bias)	Low risk	**Trial registration (prospective):** NCT00126334 One outcome planned in the trial registration was not reported, but it was not a main outcome, viz in-hospital acute renal insufficiency (increase in serum creatinine ≥ 0.5 mg/dL)

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Cooper 2011 *(Continued)*

Other bias	Low risk	No other biases identified

de Almeida 2015

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site, superiority trial **Setting:** ICU, tertiary oncology university teaching hospital, São Paulo, Brazil **Recruitment:** January 2012 to July 2012 **Maximum follow-up:** 30 days
Participants	Adult participants who underwent a major surgical procedure for abdominal cancer and required post-operative care in the ICU • Liberal: n = 97; mean age (SD) = 64 (14) years • Restrictive: n = 101; mean age (SD) = 64 (12) years
Interventions	While in the ICU: • Liberal group: received transfusion when Hb was < 9 g/dL • Restrictive group: received transfusion when Hb was < 7 g/dL
Outcomes	**Primary outcome:** a composite of all-cause mortality or severe clinical complications within 30 days. Severe clinical complications included major cardiovascular complications, septic shock, acute kidney injury requiring renal replacement therapy, ARDS, and reoperation **Secondary measures:** length of stay in ICU, length of stay in hospital, health-related QOL, hospital costs
Notes	**Trial name:** Transfusion Requirements in Surgical Oncologic Patient (TRISOP) **Trial registration:** (prospective) NCT01502215 **Trial funding:** "Support was provided solely from institutional and/or departmental sources" (de Almeida 2015 p 37) **COI statement by investigators:** "the authors declare no competing interests" (de Almeida 2015 p 37)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... patients were randomized in a 1:1 ratio to one of two erythrocyte strategies ... After consent, the medical staff contacted the study randomization center to register the patient and to be told which group the patient was allocated to ..." (de Almeida 2015 p 30) "Allocation numbers were derived from a random number table prepared by the chief statistician and were placed in opaque envelopes and opened sequentially to determine the treatment group of the patient" (de Almeida 2015 p 30)
Allocation concealment (selection bias)	Low risk	"To avoid loss of concealment, the group to which the patient was allocated could only be accessed after registration in the study randomization center. Allocation numbers were derived from a random number table prepared by the

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de Almeida 2015 *(Continued)*

		chief statistician and were placed in opaque envelopes and opened sequentially to determine the treatment group of the patient" (de Almeida 2015 p 30)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) was not relevant, and we graded risk of bias as 'low' "The participants and the study investigators who classified outcomes and those who conducted the follow-up telephone assessments were blinded to the study-group assignments and had no access to transfusion data" (de Almeida 2015 p 30)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"The participants and the study investigators who classified outcomes and those who conducted the follow-up telephone assessments [including function] were blinded to the study-group assignments and had no access to transfusion data" (de Almeida 2015 p 30)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals or exclusions. There were 20 protocol deviations (13 in the liberal group, 7 in the restrictive group). Analysis was done by intention to treat. "If the treating clinicians transfused an additional erythrocyte unit outside the protocol, it was recorded as a protocol deviation. After ICU discharge, the decision to transfuse was left to the discretion of the physician in charge of the patient clinical care. During the 30-day follow-up period, if a patient returned to the ICU for any reason, the allocated transfusion strategy was maintained. An intention-to-treat analysis was performed and considered the patients in their originally assigned groups" (de Almeida 2015 p 30)
Selective reporting (reporting bias)	Low risk	**Trial registration:** (prospective) NCT01502215 No reporting bias was apparent
Other bias	Low risk	No other biases identified

DeZern 2016

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site pilot study **Setting:** tertiary referral centre for oncology, Baltimore, MD, USA **Recruitment:** April 2014 to July 2015 **Maximum follow-up:** 60 days
Participants	Acute leukaemia participants (acute myeloid leukaemia, acute lymphoblastic leukaemia/lymphoma, acute promyelocytic leukaemia, treatment-related myeloid neoplasm, high-grade myelodysplastic syndrome) over 18 years of age admitted to inpatient leukaemia services with plans for inpatient myelosuppressive chemotherapy • Liberal group: n = 30; mean age (IQR) = 62.5 (55.2 to 67.8) years • Restrictive group: n = 59; mean age (IQR) = 56 (45.5 to 67) years
Interventions	• Liberal group: Hb < 8-g/dL trigger • Restrictive group: Hb < 7-g/dL trigger

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DeZern 2016 *(Continued)*

	Participants randomised in 2:1 ratio favouring the restrictive group
Outcomes	**Primary outcomes:** feasibility defined a priori as achieving the following criteria: • > 50% of eligible participants consented; • > 75% of participants randomised to the 7-g/dL arm tolerated the transfusion trigger; • < 15% of participants crossed over from the lower transfusion threshold arm to the higher transfusion threshold arm; • no indications of the need to pause the study for safety concerns. **Secondary outcomes:** fatigue, bleeding, response to therapy, vital status on day 60, length of hospital stay (days), numbers of units of RBCs and PLTs transfused per participant Trial author provided 30-day mortality by telephone to Dr Carson
Notes	**Trial registration:** (prospective) NCT02086773 **Trial funding:** "... supported by a grant from the Society for the Advancement of Blood Management (SABM) sponsored by Haemonetics Corp. (Braintree, MA [USA])" [to first author of study] (DeZern 2016 p 1) **COI statement by investigators:** trial authors disclosed none (DeZern 2016 p 8)

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 groups, respectively. Blocking was used to specify a 2:1 ratio ... 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 participant in the trial. An investigator who did not enrol or provide consent for participants performed randomisation sequence and creation and numbering of the envelopes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we grade risk of bias as 'low' Detection bias was therefore low risk for the outcome of mortality (data not in published paper, supplied to current review authors by personal contact); other secondary outcomes had high risk (see below)
Blinding of outcome assessment (detection bias) Subjective measures	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; however, the similarity in fatigue scores suggests this potential bias was not a concern. Finally, 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. This bias, however, appeared to decrease over time,

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DeZern 2016 *(Continued)*

		suggesting that the change in practice to a restrictive transfusion strategy is one that can be accomplished with clinical providers adapting well to the change" (DeZern 2016 p 7)
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 participants enrolled; 80 were judged to be evaluable. Of these, 75 were transfused at goal; 3 died (deaths not attributable to transfusion); 1 stopped for cardiac ischaemia; 2 were transfused off protocol trigger; 2 withdrew consent There was an imbalance between clinician withdrawals (5 in the low arm compared with 1 in the high arm), but we judged that there was no important attrition bias
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT02086773). No reporting bias was apparent
Other bias	Low risk	No other bias was apparent

Ducrocq 2021

Study characteristics	
Methods	**Design:** RCT, open-label, multicentre, international, non-inferiority trial **Setting:** 35 hospitals in France and Spain **Recruitment:** March 2016 to September 2019 **Maximum follow-up:** 30 days (investigators plan 12 month followup; results unpublished at the time of this update)
Participants	666 participants with myocardial infarction within 48 hours of onset of symptoms, Hb between 7 g/dL and 10 g/dL, with healthcare insurance. Excluded were those with cardiogenic shock, post PCI or CABG, transfusion in previous 30 days, any known haematological disease, or massive bleeding • Liberal group: n = 324; M/F = 184/140; age = 76 (IQR 69 to 84) • Restrictive group: n = 342; M/F = 201/141; age = 78 (IQR 69 to 85)
Interventions	• Liberal group: received transfusion when Hb < 10 g/dL with target > 11 g/dL • Restrictive group: received transfusion when Hb < 8 g/dL with target 8 g/dL to 10 g/dL
Outcomes	**Primary outcome:** cost-effectiveness **Secondary outcome:** the outcome of greatest clinical interest was MACE, defined as the composite of all cause 30-day mortality, recurrent myocardial infarction, stroke, or emergency revascularisation for ischaemia
Notes	**Trial title:** Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial **Trial registration:** NCT02648113 **Trial funding:** "... the trial was designed by the French Alliance for Cardiovascular Trials and was funded via a grant from the Programme de Recherche Médico-Economique (PRME) 2015 from the French Ministry of Health and a grant from the Instituto de Salud Carlos III (Spanish Ministry of Economy and Competitiveness: grant PI15/01543). There was no industry support. ... The funders and sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication" (Ducrocq 2021 p 559)

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Ducrocq 2021 *(Continued)*

COI statement by investigators: Dr. Danchin reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Intercept, MSD, Novo Nordisk, Pfizer, Sanofi, Servier, UCB, and Vifor outside the submitted work. Dr. Ducrocq reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen, Sanofi, and Terumo outside the submitted work. Dr. Durand-Zaleski reported receiving grants from the Ministry of Health during the conduct of the study and personal fees from Vifor outside the submitted work, and being the chair of the scientific committee of the French Blood Establishment. Dr. Lemesle reported receiving personal fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, MSD, Mylan, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, and Servier outside the submitted work. ... " (for further disclosures: see Ducrocq 2021 p 559)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Centralized blocked randomization list will be prepared by the statisticians of the clinical research Unit (URC-EST). The investigators at each site ...obtain[ed] the randomized strategy allocation using Internet (CleanWeb, Telemedecin Technologies, S.A.S). CleanWeb will assign the patient a unique randomization number that corresponds to one of the two transfusion strategies"
Allocation concealment (selection bias)	Low risk	Web-based with varying block sizes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "The choice of an open label design is justified by the difficulty in blinding the intervention (blood transfusion) and by the fact that the clinical outcomes are "hard" outcomes (mortality and non-fatal major cardiac events) adjudicated by a critical event committee, blinded to randomization, and the Hb levels" (Ducrocq 2021, Supplement 1, p 19)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	668 were randomised; 2 were excluded due to lack of consent/re-consent; 666 were randomised with consent. All participants were included in as-randomised analysis; 327/342 were included in as-treated analysis for restrictive strategy arm; 322/324 were included in as-treated analysis
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT02648113), and both the protocol and the trial statistical analysis plan were made publicly available. No reporting bias was apparent
Other bias	Low risk	None detected

Fan 2014

Study characteristics

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Fan 2014 *(Continued)*

Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** tertiary (university teaching hospital), Nanjing, China **Recruitment:** October 2011 to May 2013 **Maximum follow-up:** in-hospital stay
Participants	192 randomised 186 participants analysed, 65 years of age or older, undergoing elective unilateral total hip replacement • Liberal group: n = 92; mean (SD) age = 75 (6) years • Restrictive group: n = 94; mean (SD) age = 73 (7) years
Interventions	• Liberal group: received transfusion to maintain Hb > 10 g/dL • Restrictive group: received transfusion with Hb < 8 g/dL or when symptoms of anaemia developed
Outcomes	Postoperative delirium, cerebrovascular accident, cardiac failure, myocardial infarction, pulmonary embolism, pneumonia, superficial wound infection, urinary tract infection, acute renal failure
Notes	**Trial registration:** none ascertainable **Trial funding:** work was supported by grants from the National Natural Science Foundation of China (No. 81300946) and the Natural Science Foundation of Jiangsu Province (BK2012778) **COI statement by investigators:** "there is no conflict of interest to be stated" (Fan 2014 p 184)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to the restrictive or liberal transfusion strategy group using a random number table and a sealed envelope technique" (Fan 2014 p 182)
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to the restrictive or liberal transfusion strategy group using a random number table and a sealed envelope technique" (Fan 2014 p 182)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of outcome assessment was not described. Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'. We have also considered outcomes such as pneumonia, requiring radiological investigations as a hard outcome
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	Blinding of outcome assessment was not described for assessments of cognition and delirium. We considered risk of bias as low, given the structured assessment

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Fan 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	192 participants were randomised. Data were included for 94/96 in the restrictive group (2 excluded as declined transfusion). Data were included for 92/96 in the liberal group (4 excluded as declined transfusion)
Selective reporting (reporting bias)	Low risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other bias was apparent. Study sample size might be considered small for the outcomes

Foss 2009

Study characteristics	
Methods	**Design:** RCT, parallel, single-site trial **Setting:** university teaching hospital, Denmark **Recruitment:** February 2004 to July 2006 **Maximum follow-up:** 30 days (for mortality); ambulatory capacity (the primary outcome) was assessed at 3 days
Participants	120 hip fracture participants were randomly allocated: • Liberal group: n = 60; M/F = 14/46; mean (SD) age = 81 (6.8) years • Restrictive group: n = 60; M/F = 14/46; mean (SD) age = 81 (7.3) years
Interventions	• Liberal group: received packed RBCs when Hb dropped to < 10.0 g/dL • Restrictive group: received packed RBCs when Hb dropped to < 8.0 g/dL
Outcomes	Ambulatory capacity (measured by Cumulated Ambulatory Score), mortality, length of stay, cardiac complications, infectious complications
Notes	**Trial registration:** NCT00162617 **Trial funding:** received financial support from IMK-Almene fond (Denmark) **COI statement by investigators:** "the authors have no conflicts of interest" (Foss 2009 p 227)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization was done via a computer generated list by a person not affiliated with the project" (Foss 2009 p 228)
Allocation concealment (selection bias)	Low risk	"Upon inclusion, the sealed envelope, containing the transfusion threshold and with the patient's study number on it, was placed in the patient charts next to the transfusion papers concealing the allocation to both the patient and the physiotherapists conducting the ambulation assessments, making the study double-blind" (Foss 2009 p 228)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention was not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'

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Foss 2009 *(Continued)*

Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "....30-day mortality were registered, the latter established via the Danish civil registry" (Foss 2009 p 229)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	The physiotherapist who performed ambulation assessment was blinded ".... concealing the allocation to both the patient and the physiotherapists conducting the ambulation assessments, making the study double-blind" (Foss 2009 p 228)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 of 100 participants did not have ambulation assessment (54/60 included in per-protocol analysis of liberal transfusion; 53/60 in restrictive transfusion)
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT00162617). No reporting bias was apparent
Other bias	Low risk	No other biases were apparent

Gillies 2020

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, feasibility trial **Setting:** acute university teaching hospital (Scotland, UK) **Recruitment:** November 2017 to January 2019 **Maximum follow-up:** 30 days
Participants	62 participants > 50 years of age with hip fracture admitted to single centre within 48 hours before surgery • Liberal group: n = 26; M/F = 8/18; mean age (SD) = 82 (11) years • Restrictive group: n = 36; M/F = 10/26; mean age (SD) = 82 (11) year
Interventions	• Liberal group: transfused when Hb was < 9.0 g/dL with target Hb range of 9.0 g/dL to 11.0 g/dL • Restrictive group: transfused when Hb was < 7.0 g/dL with target Hb range of 7.0 g/dL to 9.0 g/dL Participants were transfused with 1 unit of RBCs at a time, and Hb was re-checked until within the target range
Outcomes	**Primary outcomes:** related to feasibility of the trial; included proportion of eligible patients recruited; protocol compliance; Hb distribution within 3 and 30 days of surgery (including nadir haemoglobin); red blood cell use within 5 days of anaemia, and within 30 days of surgery or hospital discharge **Primary clinical outcome:** postoperative myocardial injury, defined as elevated high-sensitivity troponin concentration above upper reference limit during the trial period **Secondary clinical outcomes:** mortality at 30 and 60 days, acute kidney injury (KDIGO definition), delirium, myocardial infarction (universal definition), major adverse cardiac events (MACE), postoperative complications
Notes	**Trial title:** RESULT-NOF

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Gillies 2020 *(Continued)*

Trial registration: NCT03407573 (deemed prospective: record first submitted February 2017; trial began October 2017; record first posted January 2018)

Trial funding: British Journal of Anaesthesia/Royal College Anaesthetics Grant (ID WKRO 2016 0018)

COI statement by investigators: 1 trial author: "NLM [sic] has received consultancy, research grants, and speaker fees from manufacturers of cardiac troponin testing including Abbott Diagnostics, Roche, and Singulex. All other authors declare they have no conflicts of interest" (Gillies 2020 p 9)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned 1:1 to either a restrictive or liberal transfusion strategy for the duration of their hospital stay or 30 days, whichever was sooner. A secure electronic Internet-based randomisation system was used with a dynamically allocated block list (block sizes 4 and 6) ..." (Gillies 2020 p 3)
Allocation concealment (selection bias)	Low risk	"Secure Internet-based system ... The patient's clinical team and the hospital blood transfusion laboratory were informed of the patient's study status by the study team, having been concealed until that point, and that they were to be transfused according to the study protocol" (Gillies 2020 p 3)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "The clinical and research teams were not blinded to the intervention but were blinded to the primary outcome. The study statistician analysed data blinded from group allocation. The adjudicators who assessed ECGs and other data used to assess cardiovascular outcomes were also blinded" (Gillies 2020 p 3)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"The clinical and research teams were not blinded to the intervention but were blinded to the primary outcome. The study statistician analysed data blinded from group allocation. The adjudicators who assessed ECGs and other data used to assess cardiovascular outcomes were also blinded" (Gillies 2020 p 3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was complete for 26/26 in the liberal transfusion group; for 34/36 in the restrictive group
Selective reporting (reporting bias)	Low risk	Trial registration: NCT03407573. Record deemed prospective (see 'notes' above). All prespecified outcomes reported in the paper
Other bias	Low risk	Protocol violations noted - 81% liberal compliance, 64% restrictive compliance "There was a higher prevalence of cardiovascular risk factors in participants who became anaemic compared with those who did not" (Gillies 2020 p 5), but this was considered acceptable for a feasibility trial

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Gobatto 2019

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** 2 ICUs within a university teaching hospital, Brazil **Recruitment:** August 2014 to June 2016 **Maximum follow-up:** 6 months
Participants	Participants over 18 years of age admitted to the ICU with moderate or severe traumatic brain injury (Glasgow Coma Scale (GCS) score ≤ 12 at hospital admission) with Hb < 9 g/dL within 7 days of hospital admission 47 participants randomised; 44 in analysis • Liberal group: n = 21; M/F = 20/1; mean age (SD) = 33 (11.0) years • Restrictive group: n = 23; M/F = 20/3; mean age (SD) = 36 (15.0) years
Interventions	• Liberal group: transfused if Hb was < 9 g/dL • Restrictive group: transfused if Hb was < 7 g/dL
Outcomes	**Primary outcome:** difference in mean Hb between liberal and restrictive groups during the 14 days after hospital admission **Secondary outcomes:** ICU mortality; hospital mortality; mortality at 6 months after hospital discharge; adverse events; presence of elevated intracranial pressure and intensity of intracranial hypertension treatment; cerebral haemodynamic findings on sequential transcranial Doppler ultrasound analysis; lengths of ICU and hospital stay; ICU-free days; duration of mechanical ventilation; mechanical ventilation-free days; neurological status at hospital discharge and 6 months after hospital discharge (GOS)
Notes	**Trial name:** Transfusion Requirements After Head Trauma (TRAHT) **Trial registration (prospective):** NCT0220329 **Trial funding:** "the study was not financially supported by any funding source. The design, collection, analysis and the interpretation of data, plus the writing and the publication of the manuscript, were done by the authors without participation or influence from any funding source" (Gobatto 2019 p 9) **COI statement by investigators:** "the authors declare that they have no competing interests" (Gobatto 2019 p 9)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Enrolled patients were randomized in a 1:1 ratio to the restrictive or the liberal arm in random permuted blocks. The randomization was performed using an automated third party Internet-based service (Sealed Envelope, London, UK) in order to maintain allocation concealment" (Gobatto 2019 p 2)
Allocation concealment (selection bias)	Low risk	"The randomization was performed using an automated third party Internet-based service (Sealed Envelope, London, UK) in order to maintain allocation concealment" (Gobatto 2019 p 2)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'

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Gobatto 2019 *(Continued)*

Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'. In this trial, the primary outcome was change in haemoglobin - a laboratory measure and a hard outcome "None of the investigators or ICU staff members was aware of the randomization list prior to group allocation, or of the block numbers or block sizes, at any time ... be blinded to the treatment assignments" (Gobatto 2019 p 2)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"None of the investigators or ICU staff members was aware of the randomization list prior to group allocation, or of the block numbers or block sizes, at any time ... Given the nature of the intervention, the ICU staff could not be blinded to the treatment assignments" (Gobatto 2019 p 2) Primary outcome was change in haemoglobin level, but neurological outcomes were also assessed; we consider risk of bias to be low due to the above measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	47 participants were randomised; in the restrictive strategy arm, there was 1 exclusion due to a 'randomization error'; in the liberal strategy arm, there were 2 exclusions due to withdrawal of consent and to 1 randomisation [sic] (error) (Gobatto 2019 p 4)
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT02203292). No reporting bias was apparent (all prespecified outcomes reported in the paper)
Other bias	Unclear risk	Some baseline imbalances (e.g. pupil alterations, computed tomography changes, use of blood prerandomisation)

Gregersen 2015

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** orthopaedic ward in a university teaching hospital, Denmark **Recruitment:** January 2010 to June 2013 **Maximum follow-up:** 12 months
Participants	284 participants aged 65 years or older undergoing hip fracture surgery who had postoperative Hb between 9.7 g/dL and 11.3 g/dL during the first 6 days postoperatively • Liberal group: n = 140; mean age (SD) = 88 (6.9) years • Restrictive group: n = 144; mean age (SD) = 86 (6.8) years
Interventions	• Liberal group: received transfusion when Hb was < 11.3 g/dL • Restrictive group: received transfusion when Hb was < 9.7 g/dL
Outcomes	**Primary outcomes:** recovery from physical disabilities (3 tools were used to measure physical performance: the Modified Barthel index, New Mobility score, and Cumulated Ambulation Score); total number of infections (pneumonia, urinary tract infection, other); cognition; delirium (10 days); depression; quality of life; modified Barthel Index; comprehensive frailty index Death within 30 days provided (together with causes, e.g. sepsis, cardiovascular disease, pneumonia)
Notes	Four publications reported results **Trial title:** Transfusion Requirements In Frail Elderly (TRIFE)

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Gregersen 2015 *(Continued)*

Trial registration: NCT01102010

Trial funding: "we have received grants from the Helga and Peter Korning Foundation for medical equipment (HemoCue portable photometer). Costs of data collection, analyses, and article writing were borne by the Department of Geriatrics at Aarhus University Hospital" (Gregersen 2015 p 7)

COI statement by investigators: "the authors declare that there is no conflict of interest" (Gregersen 2015 p 7)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization procedure was provided by an allocation concealment process and conducted electronically in the web-based clinical-trial-support-system 'TrialPartner' from Public Health and Quality Improvement in Central Denmark Region. This central computer program using permuted block-sizes stratified the randomization according to gender and type of residence. Results of randomization were available at the electronic patient record for the hospital staff in the Orthopedic and Geriatric wards since the staff should administer the transfusions" (Gregersen 2015 p 2)
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"The participants, their relatives, and the endpoint assessors were blinded to the result of randomization" (Gregersen 2015 p 2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 284 participants, there were 8 dropouts (4 from each group - reasons cited as refusing transfusion and 1 acute bleeding ulcer) and 8 further protocol deviations per transfusion group
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT01102010). No reporting bias was apparent
Other bias	Low risk	No other biases were apparent

Grover 2006

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, multicentre equivalence trial **Setting:** 3 acute hospitals in southeast England, UK **Recruitment:** not stated **Maximum follow-up:** in-hospital stay

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Grover 2006 *(Continued)*

Participants	260 participants undergoing elective lower limb joint replacement surgery randomly allocated to 1 of 2 groups: • Liberal group: n = 109; M/F = 55/54; mean (SD) age = 71.5 (7.6) years • Restrictive group: n = 109; M/F = 48/61; mean (SD) age = 70.7 (7.1) years
Interventions	• Liberal group: received packed RBCs when Hb dropped to < 10.0 g/dL; maintained Hb between 10.0 g/dL and 12.0 g/dL • Restrictive group: received packed RBCs when Hb dropped to < 8.0 g/dL; maintained Hb between 8.0 g/dL and 9.5 g/dL
Outcomes	Ischaemic load, blood load, Hb, number of units transfused, length of hospital stay, adverse events, new infections requiring antibiotic therapy
Notes	**Trial registration:** none ascertainable **Trial funding:** NHS/NBS National Research Review Committee (UK) **COI statement by investigators:** nothing reported in the published paper concerning this issue

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized preoperatively using permuted blocks that were derived from random number tables" (Grover 2006 p 107)
Allocation concealment (selection bias)	Low risk	"Envelopes containing the number and allocation sequence remained sealed until the patient was assigned to intervention" (Grover 2006 p 107)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "The patient and technician analysing the Holter tapes were unaware of treatment allocation. The anaesthetists and surgical team responsible for the patient were informed of treatment allocation" (Grover 2006 p 107)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 260 participants recruited (from a planned target of 660), outcome data were presented for 218. The missing 42 participants did not have analysable Holter tape recordings
Selective reporting (reporting bias)	Unclear risk	Evidence of prospective registration/trial protocol unavailable, so insufficient information on which to make a judgement
Other bias	Unclear risk	"Unfortunately, the study recruited only 260 participants, from a target of 660 to achieve sufficient statistical power. As recruitment commenced it became clear that the strict exclusion criteria, specifically the ECG criteria, meant that the proportion of patients eligible to participate in the study was much lower

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Grover 2006 *(Continued)*

	than anticipated. This, in turn, prolonged the time during which recruitment took place. With a fixed amount of funding and time available to research fellows in subspecialty training in England, the study had to be curtailed after 2 years"

Hajjar 2010

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, non-inferiority trial **Setting:** ICU at university hospital cardiac surgery referral centre in Brazil **Recruitment:** February 2009 to February 2010 **Maximum follow-up:** 30 days
Participants	512 adult participants who underwent cardiac surgery with cardiopulmonary bypass • Liberal group: n = 257; M/F = 161/92; mean (SD) age = 60.7 (12.5) years • Restrictive group: n = 255; M/F = 149/100; mean (SD) age = 58.6 (12.5) years
Interventions	• Liberal group: transfused with RBCs if Hct was < 30% at any time from the start of surgery until discharge from the ICU • Restrictive group: transfused if Hct was < 24%
Outcomes	**Primary outcome composite endpoint:** 30-day all-cause mortality and severe morbidity (cardiogenic shock; ARDS or acute renal injury requiring dialysis or haemofiltration; respiratory, cardiac, neurological, and infectious complications; inflammatory complications; bleeding; ICU and hospital lengths of stay, RBC transfusions) Confusion assessment scale was used daily in those who presented with delirium
Notes	**Trial title:** Transfusion Requirements After Cardiac Surgery: The TRACS Randomized Controlled Trial **Trial registration** (not prospective; recruitment began in February, registration posted in November 2009): NCT01021631 **Trial funding:** none mentioned in main trial publication nor in NCT record **COI statement by investigators:** "financial disclosures: none reported" (Hajjar 2010 p 1567)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to a liberal or a restrictive transfusion strategy. Opaque envelopes arranged using a random-number table were prepared by the chief statistician and opened sequentially to determine the patient's treatment group" (Hajjar 2010 p 1560)
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'

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Hajjar 2010 *(Continued)*

Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "The patient and outcome assessors were blinded to group assignment" (Hajjar 2010 p 1560)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	"Information about the treatment strategy was given to the anesthesiologist and to health care workers in the intensive care unit (ICU). The patient and outcome assessors were blinded to group assignment" (Hajjar 2010 p 3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was undertaken. Follow-up was high (512 randomised/502 in analysis; losses relatively equal - 4/257 vs 6/255 - between groups)
Selective reporting (reporting bias)	Low risk	No reporting bias was apparent, but the trial was not prospectively registered (recruitment began 9 months before study registration (NCT01021631)) Confusion Assessment Scale was briefly described on pp 1563-4 in section on 'neurologic complications' data
Other bias	Low risk	No other biases were apparent

Hébert 1995

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre pilot trial **Setting:** 5 tertiary-level ICUs, in Canada **Recruitment:** March 1993 to January 1994 **Maximum follow-up:** in-hospital stay
Participants	69 normovolaemic critically ill participants admitted to 1 of 5 tertiary-level ICUs with Hb values < 9.0 g/dL within 72 hours of admission were randomly assigned to 1 of 2 groups: • Liberal group: n = 36; M/F = 19/17; mean (SD) age = 59 (21) years • Restrictive group: n = 33; M/F = 14/19; mean (SD) age = 58 (15) years
Interventions	• Liberal group: transfused if Hb fell to between 10.0 g/dL and 10.5 g/dL. Hb maintained between 10.0 g/dL and 12.0 g/dL • Restrictive group: transfused if Hb fell to between 7.0 g/dL and 7.5 g/dL. Hb maintained between 7.0 g/dL and 9.0 g/dL
Outcomes	Mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, Hb
Notes	**Trial title:** Transfusion Requirements in Critical Care (TRICC) Pilot Study **Trial registration:** none ascertainable **Trial funding:** this work was supported by the Canadian Red Cross Society, Blood Services, Ottawa, Ontario, and the Physicians' Services Incorporated, North York, Ontario **COI statement by investigators:** none referred to in published paper
Risk of bias	

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Hébert 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were assigned to 1 of 2 groups by consecutive allocation from a random listing stratified by centre and disease severity ... blocked by balanced groups of 10" (Hébert 1995 p 1440)
Allocation concealment (selection bias)	Unclear risk	Trial reported no information regarding this domain
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All randomized patients completed the study" (Hébert 1995 p 1440)
Selective reporting (reporting bias)	Unclear risk	Evidence of prospective registration/trial protocol unavailable; insufficient information available to make a judgement
Other bias	Low risk	No other biases were apparent

Hébert 1999

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre trial **Setting:** 22 tertiary-level and 3 community ICUs in Canada **Recruitment:** November 1994 to November 1997 **Maximum follow-up:** 30 days
Participants	838 critically ill participants with euvolaemia after initial treatment and with Hb < 9.0 g/dL within 72 hours after admission to the ICU were randomly assigned to 1 of 2 groups: • Liberal group: n = 420; M/F = 255/165; mean (SD) age = 58.1 (18.3) years • Restrictive group: n = 418; M/F = 269/149; mean (SD) age = 57.1 (18.1) years
Interventions	• Liberal group: transfused when Hb fell to < 10.0 g/dL. Hb maintained between 10.0 g/dL and 12.0 g/dL • Restrictive group: transfused if Hb dropped to < 7.0 g/dL. Hb was maintained between 7.0 g/dL and 9.0 g/dL
Outcomes	Mortality, length of hospital stay, length of ICU stay, blood usage (units), complications, infection rates, cardiac events, pulmonary oedema, pneumonia
Notes	**Trial registration:** none ascertainable

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Hébert 1999 *(Continued)*

Trial funding: supported by the Medical Research Council of Canada and by an unrestricted grant from Bayer

COI statement by investigators: published paper included no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random order was computer generated (Hébert 1999 p 410)
Allocation concealment (selection bias)	Low risk	"The data coordinating centre prepared sealed opaque envelopes, which they distributed to each participating institution where they were opened up sequentially to determine the participants treatment assignment. The envelopes were returned periodically to the coordinating centre for auditing" (Hébert 1999 p 410)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "It was not feasible to mask the assigned transfusion strategy from health care providers" Participants were ICU patients. Most outcomes were based on laboratory measures
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 838 participants randomised, there were 4 withdrawals from the liberal transfusion arm and 5 from the restrictive arm
Selective reporting (reporting bias)	Unclear risk	Evidence of prospective registration/trial protocol unavailable; insufficient information available to make a judgement
Other bias	Low risk	No other biases were apparent

Hoff 2011

Study characteristics

Methods	**Design:** 2 RCTs, parallel 2-arm, multicentre trial (DAHANCA 7 is a follow-on trial from DAHANCA 5, undertaken to extend its usefulness) **Setting:** multiple oncology departments in Denmark **Recruitment:** January 1986 to September 1990 (DAHANCA 5) and January 1992 and October 1997 (DAHANCA 7) **Maximum follow-up:** 5 years or until death

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Hoff 2011 *(Continued)*

Participants	People with diagnosed invasive squamous cell carcinoma of the supraglottic larynx or pharynx and oral cavity, with no evidence of distant metastases Participants were stratified before randomisation according to sex, institution, site of tumour, tumour status, and haemoglobin status **DAHANCA 5** assessed effects of the hypoxic radiosensitiser nimorazole plus radiotherapy vs placebo plus radiotherapy, and contained a subrandomised group of trial participants presenting with condition-specific low Hb to either transfusion or no transfusion **DAHANCA 7** assessed effects of the same dose of nimorazole given with 5 fractions of radiotherapy/week vs 6 fractions of radiotherapy/week. In this trial, again, all participants presenting with a condition-specific low Hb were subrandomised to transfusion or no transfusion **Trial flow:** within the original DAHANCA 5 trial (n = 414), 171 participants with low pre-irradiation Hb (women < 13 g/dL; men < 14.5 g/dL) were randomised to receive or not receive transfusion before final randomisation to nimazorole vs placebo. Within the DAHANCA 7 trial (n = 786), 321 participants with low haemoglobin (as above) were randomised to different regimens of administration of nimazorole (5 vs 6 radiotherapy fractions per week) Of the 492 participants from both trials, 26 were not randomised (no reason given); 1 participant in the no-transfusion group was 'in the wrong strata' and was not considered evaluable Analysis included: • Liberal group: n = 235; M/F: 195/35; 50% were ≥ 60 years old and 50% < 60 years old • Restrictive group: n = 231; M/F: 195/35; 50% were ≥ 60 years old and 50% < 60 years old
Interventions	• Liberal group: received transfusion • Restrictive group: received no transfusion For those who met the criteria for low Hb, transfusions were given with packed RBCs to achieve Hb in the 'high' value range (1 unit at a time; without leucocyte depletion as standard). If during treatment, Hb fell below the values indicated above, transfusion was repeated. Haemoglobin level was measured every fortnight
Outcomes	**Primary outcome (both** trials**):** locoregional control after radiotherapy (defined as complete and persistent disappearance of disease in the primary tumour site and also the regional lymph nodes) **Secondary outcomes:** local and regional control (with and without salvage surgery), overall survival, early and late treatment-related morbidity The influence of haemoglobin on tumour response to irradiation was also a stated goal (Overgaard 1998 p 136)
Notes	**Trial registration:** none confirmed **Trials (original trials and analyses) funding:** sources of support included the Danish Cancer Society; Legatstiftelsen, Pedersholm and the Danish Cancer Society; Clinical Resarch Unit at Aarhus Oncological Centre; the Lundbeck Foundation Center for Interventional Reseach in Radiation Oncology; and the Danish Council for Strategic Research **COI statement by investigators:** no conflicts of interest reported by trial authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In patients where all eligibility criteria were fulfilled, patient data was entered into a local computer which generated the correct strata and randomization number and at the same time printed a confirmation letter which was sent to the data center ... " (Overgaard 1998 p 136)

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Hoff 2011 *(Continued)*

		Procedures for the later trial (DAHANCA 7) are described as similar, although here, it is noted that randomisation confirmation was made by telephone, not by letter (Overgaard 2003)
Allocation concealment (selection bias)	Low risk	"Each center was supplied with sealed envelopes indicating the randomization code. These envelopes were kept outside the radiotherapy department (at the hospital pharmacy) and could only be reached in the case of a clinical situation where knowledge of the presence of active drug was crucial for the further treatment of the patient. This did not happen in the present study and all envelopes were returned intact to the data center after completion of the trial. The trial has been maintained blinded during followup and the involved institutions are still unaware of which drug treatment the individual patients received" (Overgaard 1998 p 136) No details of allocation concealment were given for the later trial, but as was already mentioned, procedures were described as similar
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for the pharmacological component of DAHANCA 5 was manifestly met (see above) and could not be met for DAHANCA 7 (where the intervention involved number of doses). Blinding of the transfusion component of both trials was, as ever, not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), risk of bias remains 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant. In addition, we note that "all diagnostic, therapeutic and follow-up data were validated and processed by the DAHANCA data center. To optimize the data quality, the events recorded were crosschecked with the hospital records to ensure correct registration of the site or sites of failure and course of death" (Overgaard 1998 p 138)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from 465 of 466 participants randomised were used within the analysis
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Unclear risk	DAHANCA 5: no other biases noted DAHANCA 6: "when the recruitment number was reached in October 1997, it became apparent that the number of patients with glottic tumours would not express enough events to secure a conclusive outcome in this groups of patients. We closed the DAHANCA 7 protocol ..." (Overgaard 2003)

Holst 2014

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre trial **Setting:** 32 general ICUs in Denmark, Sweden, Norway, and Finland **Recruitment:** December 2011 to December 2013

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Holst 2014 *(Continued)*

	Maximum follow-up: 12 months
Participants	1005 participants with septic shock and Hb < 9 g/dL were randomised • Liberal group: n = 496; age (interquartile range) = 67 (58 to 75) years • Restrictive group: n = 502; age (interquartile range) = 67 (57 to 73) years
Interventions	• Liberal group: transfused with single units of cross-matched, prestorage leuco-reduced RBCs when Hb decreased to ≤ 9 g/dL • Restrictive group: transfused with single units of cross-matched, prestorage leuco-reduced RBCs when Hb decreased to ≤ 7 g/dL The intervention period was the entire ICU stay, to a maximum of 90 days after randomisation
Outcomes	**Primary outcome:** 90-day mortality
Notes	**Trial registration:** NCT01485315 **Trial funding:** supported by a grant (09-066938) from the Danish Strategic Research Council and by Copenhagen University Hospital, Rigshospitalet, the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (ACTA Foundation), and Ehrenreich's Foundation **COI statement by investigators:** "Dr. Johansson reports receiving grant support from Pharmacosmos; and Dr. Perner, receiving grant support from CSL Behring, Fresenius Kabi, Cosmed, and Bioporto Diagnostics, and lecture fees from LFB. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org" (Holst 2014 p 10)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A centralised computer generated the assignment sequence. Randomization was performed with the use of a centralized computer generated assignment sequence, with stratification according to study site and the presence or absence of active hematologic cancer ... Patients with septic shock were randomly assigned in a 1:1 ratio, with the use of permuted blocks of varying sizes of 6, 8, or 10, to blood transfusion at the higher haemoglobin threshold or the lower haemoglobin threshold" (Holst 2014 p 10)
Allocation concealment (selection bias)	Low risk	Use of a centralised computer ensured allocation concealment. See above
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' "Treatment assignments were concealed from the investigators assessing mortality, the data and safety monitoring committee, and the trial statistician" (Holst 2014 p 10)
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)

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Holst 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	99.8% (998) included in all analyses of mortality; (977) 97.7% included in analyses of all outcomes
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT01485315). Reporting was comprehensive for 90-day outcomes in Holst 2014; longer-term data appear to have been fully reported in Rygård 2016
Other bias	Low risk	No other sources of bias were apparent

Jairath 2015

Study characteristics	
Methods	**Design:** RCT, pragmatic, open-label, feasibility, cluster design trial **Setting:** 6 university teaching hospitals in the UK **Recruitment:** September 2012 to March 2013 **Maximum follow-up:** 28 days
Participants	6 clusters including 936 participants. This trial did not require participants to meet a haemoglobin threshold for enrolment Participants were 18 years of age or older and were admitted to 1 of the participating hospitals with upper GI bleeding Participants with exsanguinating haemorrhage were excluded. Participants consented to permit data collection and follow-up • Liberal threshold: n = 533; mean (SD) age = 60.4 (20.0) years • Restrictive threshold: n = 403; mean (SD) age = 58.0 (20.3) years
Interventions	• Liberal group: 10 g/dL threshold • Restrictive group: 8 g/dL threshold
Outcomes	**Feasibility outcomes included:** recruitment rates, adherence to transfusion policy, difference in Hb, RBC exposure, evidence for selection bias **Clinical outcomes included:** further bleeding, thromboembolic and ischaemic events, number of infections, mortality, serious adverse events, health-related quality of life
Notes	**Trial title:** Transfusion in Gastrointestinal Bleeding (TRIGGER) **Trial registration (prospective):** ISRCTN85757829 **Trial funding:** NHS Blood and Transplant Research and Development **COI statement by investigators:** "we declare no competing interests" (p 144)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We randomly allocated (using a computer-generated randomisation sequence) centres to a transfusion policy using a random permuted block of six

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Jairath 2015 *(Continued)*

		(three hospitals per policy), without stratification or matching (randomisation done by BCK)"
Allocation concealment (selection bias)	High risk	"All clinicians, patients, and outcome assessors were unmasked to treatment allocation" (Jairath 2015 p 2)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' "TRIGGER was an open-label cluster randomised trial whose primary outcome was further bleeding. Because of the cluster randomisation, all researchers in a hospital were aware of treatment allocation and so could not perform a blinded assessment. A blinded adjudication committee was also not feasible as it was impossible to compile relevant information to send to the committee in a blinded manner. Therefore, the definition of further bleeding was modified to exclude subjective aspects (such as whether symptoms like vomiting blood were severe enough to indicate the outcome had been met), leaving only objective aspects (the presence versus absence of active bleeding in the upper gastrointestinal tract confirmed by an internal examination)"
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	Quality of life measures were reported. As described above, blinding was not possible for a cluster trial, and it is unclear how assessors could use this information in a selective way
Incomplete outcome data (attrition bias) All outcomes	Low risk	533 were enrolled in the liberal arm, 403 in the restrictive arm. All participants were analysed for feasibility outcomes. 512/533 of one arm and 393/403 were analysed for further bleeding at 28 days. The intraclass correlation coefficient (ICC) was very low (0.0001) for the outcome of mortality; we therefore included data considering the participant as the unit of randomisation and ignored clustering, but we performed a sensitivity analysis excluding this trial to see what effect, if any, it had on the analysis Rates of return for EQ-5D data at 28 days (by telephone) were low (237/533 and 267/403), but these results were as expected for this patient population
Selective reporting (reporting bias)	Unclear risk	Trial was prospectively registered. No reporting bias was apparent
Other bias	Low risk	No other biases noted

Jansen 2020

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, non-inferiority trial **Setting:** 3 sites (1 university and 2 general hospitals) in the Netherlands **Recruitment:** July 2002 to August 2004 **Maximum follow-up:** 12 months

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Jansen 2020 *(Continued)*

Participants	19 adult participants (≥ 18 years of age) with diagnosed myelodysplasia according to the French-American-British classification and dependent on RBC transfusion (e.g. who had ≥ 1 RBC transfusion recently) • Liberal group: n = 9; mean (SD) age = 74.9 (range 66 to 80) years • Restrictive group: n = 10; mean (SD) age = 75.7 (range 52 to 91) years
Interventions	• Liberal group: used Hb transfusion trigger < 6.0 mmoL/L (< 9.7 g/dL) • Restrictive group: used Hb transfusion trigger < 4.5 mmoL/L (< 7.3 g/dL)
Outcomes	**Primary endpoint:** physical fatigue, measured with the Multidimensional Fatigue Inventory
Notes	**Trial registration (post hoc, 2005):** ISRCTN43616311 **Trial funding:** no information **COI statement by investigators:** "the authors have no conflict of interest to declare"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Participants were blinded but physicians and nurses were not
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Participants were reported to be blinded, but this was not tested. Physicians and nurses were not blinded. Quality of life outcomes including fatigue were reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient data. 1 death in restrictive arm, 2 in liberal arm, but timing not provided. Follow-up was incomplete "After randomization 6 out of 10 patients (60%) from the restrictive and 5 out of 9 patients (55.5%) from the liberal arm completed or still participated when the study terminated. Reasons of study withdrawal were withdrawal of informed consent (two in the restrictive and one in the liberal arm), death (one in the restrictive and two in the liberal arm) and usage of growth factors (one patient in each arm)" Thus, the trial's primary outcome data were available for 11/19 participants
Selective reporting (reporting bias)	Unclear risk	Insufficient data; trial registration was done post hoc, and trial report was provided only in the form of a letter
Other bias	Unclear risk	Terminated prematurely

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Jansen 2020 *(Continued)*

	"The Temple study was terminated prematurely due to the slow recruitment rate with only 21 patients in three hospitals in 2 years. Patients who were still participating when the study ended, received transfusion therapy according to the guidelines of the local hospital" (Jansen 2020 p 879)

Johnson 1992

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-centre trial **Setting:** university teaching hospital, Boston (USA) **Recruitment:** not specified **Maximum follow-up:** in-hospital stay
Participants	39 autologous blood donors undergoing elective myocardial revascularisation were randomised to 1 of 2 groups: • Liberal group: n = 18; M/F = 16/2; mean (SD) age = 60.5 (6.9) years • Restrictive group: n = 20; M = 20; mean (SD) age = 58.2 (7.5) years
Interventions	• Liberal group: received blood to achieve Hct value of 32% • Restrictive (conservative) group: received blood to achieve Hct value of < 25%
Outcomes	Cardiac events, complications, postoperative blood loss, blood use (total units), allogeneic blood use (units), autologous blood use (units), all product blood use (units), number of participants receiving transfusions, mean cardiac index, mean systemic resistance, exercise capacity, Hct levels, length of ICU stay, length of hospital stay 5 days after surgery, all participants were asked to complete an exercise treadmill test. A second test was performed the following day
Notes	Funding not stated **Trial registration:** none ascertainable **Trial funding:** none specified for the trial, but 1 investigator was supported in part by Transfusion Medicine Academic Award K07HL02033 from the National Institutes of Health (Johnson 1992 p 307) **COI statement by investigators:** none appears in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"All patients giving informed consent were randomized (with the aid of a table of random numbers and an odd-even [conservative strategy-liberal strategy] designation) to one of two postoperative transfusion strategies" (Johnson 1992 p 308)
Allocation concealment (selection bias)	Unclear risk	It is unclear if assignment was concealed before randomisation
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'

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Johnson 1992 *(Continued)*

		Surgeons and anaesthesiologists were said to be blinded to the group of randomisation until the participant reached the ICU
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	No data from subjective outcomes (e.g. function). Exercise tolerance was assessed and reported, and risk of bias is considered unclear without more information on the assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data were complete for 38/39 participants (18/18 in the liberal group; 20/21 in the restrictive group)"
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases were apparent

Koch 2017

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre trial **Setting:** 2 hospitals (1 in Cleveland, OH, USA; 1 in Ahmedabad, Gujerat, India) **Recruitment:** March 2007 to August 2014 **Maximum follow-up:** 3 months
Participants	722 participants 18 years of age and older scheduled for elective isolated heart valve procedures, CABG surgery with or without valve procedures, and ascending aorta replacement performed on cardiopulmonary bypass • Liberal group: n = 363; M/F = 233/121; mean (SD) age = 60 (13) • Restrictive group: n = 363; M/F = 230/133; mean (SD) age = 59 (15)
Interventions	• Liberal group: a single unit of RBC was transfused when Hct fell to < 28% • Restrictive group: a single unit of RBC was transfused when Hct fell to < 24%
Outcomes	A multi-disciplinary Data and Safety Monitoring Board adjudicated clinical events **Primary outcome:** a composite of in-hospital postoperative morbidity and mortality, as defined for the Society of Thoracic Surgeons National Cardiac Database, which included: • in-hospital mortality or multi-system organ failure; • neurological morbidity (stroke or coma); • pulmonary morbidity (pneumonia, pulmonary embolus, or prolonged postoperative ventilation > 24 hours); • renal failure; • infectious morbidity (deep sternal wound infection or sepsis); • cardiac arrhythmia (atrial fibrillation or ventricular tachycardia, fibrillation); • asystole; • GI morbidity; • reoperation (for bleeding/tamponade, graft occlusion, valve dysfunction); and

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Koch 2017 *(Continued)*

- vascular morbidity (aortic or femoral artery dissection or acute limb ischaemia). Vascular morbidities were excluded from the composite in the primary analyses because their frequency was low

Secondary outcomes included:

- Length of ICU and postoperative hospital stays
- Number of RBC units transfused
- Individual components of the composite

Notes

Trial registration: registered - NCT00651573 - but not prospectively, because trial started in March 2007 and record was first submitted in March 2008

Trial funding: "this study was supported in part by the Gus P. Karos Registry Fund, the Kenneth Gee and Paula Shaw, PhD, Chair in Heart Research (EHB), and the Sheikh Hamdan bin Rashid Al Maktoum Distinguished Chair in Thoracic and Cardiovascular Surgery (JFS). These persons and funding organizations played no role in the collection of data or analysis and interpretation of the data, and had no right to approve or disapprove publication of the finished manuscript" (Koch 2017 p 1249)

COI statement by investigators: none reported in the publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Consenting patients meeting inclusion criteria were randomly assigned at time of surgery to a hematocrit trigger of either 24% or 28% for the duration of hospitalization. Randomization was stratified by site, using within each site randomly sized blocks of 6, 8, 10, and 12 so that at any given time, approximately equal numbers of patients were randomized into each transfusion trigger group" (Koch 2017 p 124)
Allocation concealment (selection bias)	Unclear risk	See above; no further information available
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Surgeon and patient were blinded. Personnel assessing patient outcomes were blinded to treatment assignment
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	SF-12 mental or physical scores; personnel assessing patient outcomes were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for 717/722 participants analysed
Selective reporting (reporting bias)	Unclear risk	Registration undertaken a year after enrolment began
Other bias	Low risk	No other biases were apparent

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Kola 2020

Study characteristics	
Methods	**Design:** RCT, single-centre, prospective, open-label, parallel-arm, non-inferiority trial **Setting:** tertiary care, university teaching hospital (Pondicherry, India) **Recruitment:** June 2015 to May 2017 **Maximum follow-up:** 45 days
Participants	Patients 18 years of age or older who presented to the emergency surgical unit with a diagnosis of upper GI bleeding • Liberal group: n = 112; M/F not reported; mean (SD) age = 49.8 (14.9) • Restrictive group: n =112; M/F not reported; mean (SD) age = 47.9 (14.8)
Interventions	• Liberal group: transfusion if Hb was < 8 g/dL with target Hb > 10 g/dL • Restrictive group: transfusion if Hb was < 7 g/dL with target Hb > 9 g/dL
Outcomes	**Primary outcome:** mortality. The time period was not designated, but deaths were reported as in-hospital, during follow-up, and overall mortality within follow-up of 45 days **Secondary outcomes:** number of days from admission to death, rebleeding episodes (in-hospital bleeding and rebleeding during 45-day follow-up), Hb value before death, number of sessions of endoscopic treatment, requirement for banding/sclerosant treatment, requirement of SB tube placement and duration, incidence of transfusion reaction (major/minor), dose, duration of octreotide infusion, length of hospital stay
Notes	**Trial registration:** CTRI/2017/09/009682, but not prospective. Trial appears to have been registered only in May 2017, when, it is reported, recruitment had closed. Maximum follow-up was 45 days. Study was submitted for publication in April 2020 and was accepted in June **Trial funding:** "nil"(Kola 2020 p 19) **COI statement by investigators:** "there are no conflicts of interest" (Kola 2020 p 19)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Stratified permuted block randomization was done using a computer program with randomly selected unequal block sizes of 4 and 6. Stratification was done based on variceal bleeding vs. `non-variceal` bleeding" (Kola 2020 p 14)
Allocation concealment (selection bias)	Low risk	"Allocation concealment was performed using a serially numbered opaque sealed envelope (SNOSE) technique. The envelopes were opened by the residents on duty and allocation was carried out at the time of admission of the patient" (Kola 2020 p 14)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'. Primary outcome is mortality and risk of bias is low

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Kola 2020 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported. No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Trial first recruited in 2015; finished in May 2017; registration also in May 2017
Other bias	Low risk	Investigators reported some baseline imbalances (e.g. cirrhosis), but they were not statistically significant

Lacroix 2007

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre trial **Setting:** 19 tertiary-care paediatric ICUs in 4 countries (Canada, Belgium, USA, UK) **Recruitment:** November 2001 to August 2005 **Maximum follow-up:** 30 days
Participants	648 (637 following withdrawals) stable critically ill children with Hb < 9.5 g/dL within 7 days after admission to an ICU were randomly allocated to 1 of 2 groups: • Liberal group: n = 317; M/F = 191/126; mean (SD) age = 39.6 (51.9) months • Restrictive group: n = 320; M/F = 190/130; mean (SD) age = 35.8 (46.2) months
Interventions	• Liberal group: transfused when Hb fell to < 9.5 g/dL, with target range of 11.0 g/dL to 12.0 g/dL • Restrictive group: transfused if Hb fell to < 7.0 g/dL, with target range of 8.5 g/dL to 9.5 g/dL
Outcomes	28-day mortality, sepsis, transfusion reactions, infection, length of stay
Notes	**Trial name:** Transfusion Requirements in the Pediatric Intensive Care Unit (TRIPICU) study **Trial registration (not prospective):** ISRCTN37246456 **Trial funding:** supported by grants (84300 and 130770) from the Canadian Institutes of Health Research and by grants (3348 and 3568) from the Fonds de la Recherche en Santé du Québec **COI statement by investigators:** "Drs. Lacroix and Hébert report receiving consulting fees and grant support from Johnson & Johnson; Dr. Hébert also reports receiving consulting fees and unrestricted funds from Novo Nordisk and Amgen serving as a Career Scientist of the Ontario Ministry of Health (1994–2004), and receiving unrestricted training funds from Canadian Blood Services; Dr. Hume reports being employed by the Canadian Blood Services; and Dr. Peters reports receiving consulting fees from Baxter, Xoma, and Eli Lilly. No other potential conflict of interest relevant to this article was reported" (Lacroix 2007 p 1609)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was centralized, with assignment data posted on the Internet. Patients were assigned to the study groups in blocks of 2 or 4 that were ran-

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Lacroix 2007 *(Continued)*

		domly distributed and stratified according to center and three age groups (≤28 days, 29 to 364 days, and >364 days)" (Lacroix 2007 p 1610)
Allocation concealment (selection bias)	Low risk	Allocation was Internet based and central
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' "Clinical staff and parents of the participants were aware of the assignments to study groups, but physicians, nurses, and research staff were unaware of the block-randomization strategy" (Lacroix 2007 p 1610)
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Mortality was the primary outcome. Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data for 626/648; withdrawals were more common in the restrictive than the liberal arm (7 vs 4); protocol violations were more common in the liberal than the restrictive arm (10 vs 1). Both ITT and per-protocol analyses were conducted
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent; however, trial was retrospectively registered (June 2004; when recruitment began in November 2001). ISRCTN37246456
Other bias	Low risk	No other biases were apparent

Laine 2018

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm trial **Setting:** university teaching hospital (Finland) **Recruitment:** June 2014 to December 2015 **Maximum follow-up:** 7 days after hospital
Participants	Patients undergoing non-emergency CABG, simple 1-valve (aortico mitral) replacement, or both, requiring cardiopulmonary bypass (CPB) • Liberal group: n = 40; M/F = 28/12; median (IQR) age = 64.5 (60.6-68.3) years • Restrictive group: n = 40; M/F = 29/11; median (IQR) age = 70.5 (67.8-73.2) years
Interventions	• Liberal group: transfused when Hb fell to < 10 g/dL • Restrictive group: transfused when Hb fell to < 8.0 g/dL
Outcomes	ROTEM was performed at 3 predetermined time points: before anaesthesia induction, immediately after CPB/surgery, and on the first postoperative morning

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Laine 2018 *(Continued)*

Notes	**Trial registration:** after trial was registered at the Hospital District of Helsinki and Uusimaa (§94,9.05.2014) [sic] and receiving approval from the institutional Ethics Committee for Surgery in Helsinki University Hospital 2014 (D-number 58/13/03/02/2014) **Trial funding:** this work was supported by a government grant for medical research and by the Finnish Angiological Society **COI statement by investigators:** "Dr. Laine has received congress related travel reimbursement from MSD Finland Oy. Dr. Schramko has received congress related travel reimbursement from TEM InternationalGmbH" (Laine 2018 p 132)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was done in blocks of 20" (Laine 2018 p 133) - no further information given
Allocation concealment (selection bias)	High risk	"... using closed envelopes" - no further information given (Laine 2018 p 133)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Clinical staff blinded to ROTEM results
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'. Laboratory outcomes including ROTEM results are also considered hard outcomes
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All 80 patients were included in the analyses" (Laine 2018 p 134)
Selective reporting (reporting bias)	Unclear risk	Evidence of prospective registration/trial protocol unavailable; insufficient information to make a judgement
Other bias	Low risk	None evident

Lotke 1999

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** university hospital (Pennsylvania, USA) **Recruitment:** not specified **Maximum follow-up:** 30 days

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Lotke 1999 *(Continued)*

Participants	127 participants undergoing primary TKA who elected to pre-donate blood were randomly assigned to 1 of 2 groups • Liberal group: n = 65; M/F = 19/46; mean age = 69.7 years • Restrictive group: n = 62; M/F = 20/42; mean age = 68.7 years
Interventions	• Liberal group: transfused with autologous blood immediately after TKA, beginning in the recovery room postoperatively • Restrictive group: transfused with autologous blood when Hb had fallen to < 9.0 g/dL
Outcomes	Complications, cardiac events, Hb, blood usage (units), mental confusion, lethargy, orthostatic hypotension, number of participants transfused
Notes	**Trial registration:** none ascertainable **Trial funding:** none reported **COI statement by investigators:** no information reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial used a computer random number generator
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Blinding of participants and personnel was not specified
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Assessments were made by a person blinded to the group to which the participant was assigned
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	Assessments were made by a person blinded to the group to which the participant was assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data appear to have been complete
Selective reporting (reporting bias)	Low risk	Evidence of prospective registration/trial protocol unavailable; insufficient information to make a judgement
Other bias	Low risk	No other biases were apparent

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Mazer 2017

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, multicentre, open-label, non-inferiority trial **Setting:** 73 sites in 19 countries (Australia, Brazil, Canada, China, Colombia, Denmark, Egypt, Germany, Greece, India, Israel, Malaysia, New Zealand, Romania, Singapore, South Africa, Spain, Switzerland, USA) **Recruitment:** January 2014 to March 2017 **Maximum follow-up:** 28 days
Participants	People 18 years of age or older who were scheduled to undergo cardiac surgery with CPB and who had a preoperative EuroSCORE I ≥ 6 5035 participants were randomised in the main trial; 208 had been randomised in the multicentre pilot trial 5092 participants were used in modified ITT analyses; numbers below are as for per-protocol analysis • Liberal group: n = 2430: M/F = 1586/844; mean age 72 years • Restrictive group: n = 2430; M/F = 1553/877; mean age 72 years
Interventions	• Liberal group: transfused when Hb was < 9.5 g/dL intraoperatively or postoperatively in the ICU or when Hb was < 8.5 g/dL when the patient was in the non-ICU ward • Restrictive group: transfused when Hb was < 7.5 g/dL intraoperatively or postoperatively
Outcomes	**Primary outcome:** a composite of death from any cause, non-fatal myocardial infarction, stroke, or new-onset renal failure with dialysis, occurring during the index hospitalisation from the start of surgery until either hospital discharge or 28 days after surgery, whichever occurred first **Secondary outcomes included:** components of the primary outcome, blood-product (including red-cell) transfusion, lengths of stay in the ICU and in the hospital, duration of mechanical ventilation, prolonged state of low cardiac output, infection, bowel infarction, acute kidney injury, seizure, delirium, encephalopathy
Notes	Primary results were presented per protocol rather than by intention to treat. This prespecified analysis included all participants except those who had protocol adherence < 90%, those who were withdrawn from the trial by the treating physician at any time, and those who withdrew consent **Trial title:** The Transfusion Requirements in Cardiac Surgery - TRICS III **Trial registration:** NCT02042898 **Trial funding:** supported by grants (232416 and 301852) from the Canadian Institutes of Health Research, by a grant (Kenneth J. Fyke Award, to Dr. Shehata) from the Canadian Blood Services – Health Canada, by a grant (1085942) from the National Health and Medical Research Council of Australia, and by a grant (16/353) from the Health Research Council of New Zealand **COI statement by investigators:** on file in supplementary forms at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1711818/suppl_file/nejmoa1711818_disclosures.pdf

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated random permuted blocks randomly assigned to one of two red-cell transfusion strategies, in a 1:1 ratio with the use of a concealed centralized, Web-based system, stratified according to center, with comput-

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Mazer 2017 *(Continued)*

		er-generated random permuted blocks of varying sizes from two to six" (Mazer 2017 p 2)
Allocation concealment (selection bias)	Low risk	Concealed centralised web-based system (as above)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Patients and clinical teams were not blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Outcomes were adjudicated by committee blinded to treatment assignment
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not apparent. Losses to follow-up low (5092 from 5243 patients)
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT02042898). No evidence of selective reporting
Other bias	Low risk	None evident

Murphy 2015

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, open-label, non-inferiority trial **Setting:** 17 centres (UK) **Recruitment:** July 2009 to February 2013 **Maximum follow-up:** 90 days
Participants	Participants > 16 years of age who were undergoing non-emergency cardiac surgery with Hb < 9 g/dL 2007 randomised; 4 withdrew • Liberal group: n = 1003; median age (IQR) = 70.8 (64.1 to 76.7) years • Restrictive group: n = 1000; median age (IQR) = 69.9 (63.1 to 76.0) years
Interventions	• Liberal group: received transfusion when Hb was < 9 g/dL • Restrictive group: received transfusion when Hb was < 7.5 g/dL
Outcomes	**Primary outcome:** a composite of serious infection (sepsis or wound infection) or an ischaemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) within 3 months after randomisation **Secondary outcomes included:** units transfused, infection, ischaemic events, acute kidney injury, hospital stay and ICU stay, general quality of life (using the EQ-5D), cost

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Murphy 2015 *(Continued)*

Notes	**Trial title:** TITRe2 **Trial registration (prospective):** ISRCTN70923932 **Trial funding:** "supported by the NIHR Health Technology Assessment program ... Dr. Reeves and the research nurse team in Bristol were supported in part by the NIHR Bristol Biomedical Research Unit in Cardiovascular Disease, and Drs. Murphy, Angelini, and Rogers were supported by the British Heart Foundation" (Murphy 2015 p 1007) **COI statement by investigators:** "no potential conflict of interest relevant to this article was reported" (Murphy 2015 p 1007)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to either the liberal transfusion-threshold group (threshold hemoglobin level, 9 g per deciliter) or the restrictive transfusion-threshold group (threshold hemoglobin level, 7.5 g per deciliter) by means of a secure Internet-based system that concealed assignments and used cohort minimization to balance assignments according to center and type of surgery" (Murphy 2015 p 998)
Allocation concealment (selection bias)	Low risk	Trial used an Internet-based system that concealed assignments and used cohort minimisation to balance assignments according to centre and type of surgery (Murphy 2015 p 998)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Physicians and nurses were aware of group assignments
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Outcomes were adjudicated
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	For the subjective measure of quality of life (EQ-5D), we rated risk of bias to be low, as participants were unaware of group assignment. Furthermore, investigators reported that they "tested our success in keeping the study groups blinded by asking the patients if they were aware of the group they were in" "At discharge, 15.1% of patients believed they knew treatment and 75.6% were correct" (Murphy 2015 p 1002); however, "3 months after surgery, a greater number of patients (27.5%) thought that they knew which treatment they had received, but fewer (56.6%) were correct"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were missing for the primary outcome analysis (composite as above) for 4.8% of the sample; overall data including for mortality were missing for only 1.2% at 3 months
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered, and all prespecified outcomes appear to have been reported in full
Other bias	Low risk	No other biases were apparent

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Møller 2019

Study characteristics	
Methods	**Design:** RCT, single-site, 2-arm parallel trial **Setting:** "vascular unit servicing a population of 820,000"; Denmark **Recruitment:** 2015 to 2017 **Maximum follow-up:** 90 days
Participants	58 participants over 40 years of age undergoing elective open infrarenal abdominal aortic aneurysm repair or lower limb bypass surgery or femoro-femoral cross-over surgery • Liberal group: n = 29; mean (SD) age = 73.7 (7.3.) years • Restrictive group: n = 29; mean (SD) age = 71.3 (9.4) years
Interventions	• Liberal group: transfused to maintain Hb > 9.7 g/dL • Restrictive group: transfused when Hb < 8.0 g/dL to maintain Hb ≥ 8.0 g/dL
Outcomes	**Primary outcome:** mean postoperative Hb between days 0 and 15 **Secondary outcomes:** units of RBCs transfused, randomisation rate, proportions of patients with protocol suspensions, adherence to Hb concentrations used for transfusion triggers, intraoperative tissue oxygenation determined by near-infrared spectroscopy, severe adverse events within 30 days of surgery
Notes	**Trial title:** Transfusion in Vascular surgery (TV) trial **Trial registration:** NCT02465125 **Trial funding:** Local Research Fund of Region Zealand, Næstved, Slagelse, Ringsted Hospital (2015-01-26) (A. Møller), and Region Sjaelland Health Research Fund (Denmark). The funders of this trial were reported to be public organisations with no role in trial design, collection, management, analysis, and interpretation of data, writing of the report, or the decision to submit the report for publication **COI statement by investigators:** "the authors declare no competing financial interests" (Møller 2019 p 2648)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation sequence was computer generated in a 1:1 ratio with fixed block sizes of 6 stratified for type of surgery: open abdominal aortic aneurism operation vs lower limb bypass
Allocation concealment (selection bias)	Low risk	External, centralised, web-based system
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Patients, statisticians, and outcome assessor were blinded to group assignment
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Outcome assessors were blinded to group assignment

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Møller 2019 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function) Near-infrared spectroscopy done by blinded assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	58 participants randomised. There were 8 protocol suspensions in the restrictive group and 4 in the liberal group. 10 participants in the restrictive group 'avoided' RBC transfusion; none did in the liberal group All participants were included in an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Trial reports 90 days' mortality, not 30 days (as stated on Clinicaltrials.gov) 30-Day outcomes were presented (e.g. laboratory values) and data on mortality were presented in a supplement (1 death both arms) prepublished protocol was reported
Other bias	Unclear risk	Protocol suspensions for RBC transfusion were recorded, but there was a good discussion about the definitions of protocol adherence, and this would be expected as an issue for trials in this patient population. Overall rates of non-adherence were 28% and 34% of patients in the 2 arms, which seems quite high

Nielsen 2014

Study characteristics	
Methods	**Design:** RCT, parallel, 2-centre trial. Trial authors wrote, "our study may be considered a feasibility study" (Nielsen 2014 p 8) **Setting:** orthopaedic departments at 1 university teaching hospital and 1 general hospital, Copenhagen, Denmark **Recruitment:** June 2009 to May 2011 **Maximum follow-up:** 30 days
Participants	66 participants at least 18 years of age scheduled for elective hip revision surgery • Liberal group: n = 33; median age (5% to 95% range) = 72 (54 to 89) years • Restrictive group: n = 33; median age (5% to 95% range) = 68 (43 to 86) years
Interventions	• Liberal group: received transfusion at Hb of 8.9 g/dL (5.5 mmol/L) • Restrictive group: received transfusion at Hb of 7.3 g/dL (4.5 mmol/L) Target levels of Hb were > 8.9 g/dL in the liberal group and 7.3 g/dL to 8.9 g/dL in the restrictive group
Outcomes	**Primary outcome:** 'Timed up and go' test **Other outcomes included:** pneumonia, wound infection, GI complications, dizziness, hypotension, fatigue, deep vein thrombosis, falls
Notes	**Trial registration (prospective):** NCT00906295 **Trial funding:** "the first author has received an unrestricted research grant from the TrygFonden foundation, Denmark. TrygFonden has not taken any part in designing the study, analyzing the data or approving the manuscript" (Nielsen 2014 p 8)

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Nielsen 2014 *(Continued)*

COI statement by investigators: "the authors declare that they have no competing interests" (Nielsen 2014 p 8)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A dedicated computer program (Idefix) was used after participants' baseline data were entered. Allocation was written on a form, which was kept in the investigator's office, and allocation could be accessed only by the investigator in charge of administrating RBCs
Allocation concealment (selection bias)	Low risk	Only 1 investigator had access to the programme. Investigators at the other hospital had to call this investigator to randomise
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Allocation and Hb during the testing period were concealed from participants, but the investigator, staff in the operating room, and staff at the ward could not be blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' The physiotherapist testing the participant was blinded, but it is not stated who reviewed medical records for other outcomes
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	Timed up and go test, assessed by blinded physiotherapist
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias was apparent, but patient flow identified losses to primary analysis (8 in restrictive arm, 5 in liberal arm)
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered. All prespecified outcomes were reported. No deaths were reported in either group
Other bias	Unclear risk	Transfusion threshold was never reached in around half of recruited patients

Palmieri 2017

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, phase 3, multicentre, international trial **Setting:** 18 burn centres located in 3 countries (USA (16), Canada (1), New Zealand (1)) **Recruitment:** August 2010 to August 2015 **Maximum follow-up:** mortality reported at and after 30 days; 'after' not specified
Participants	345 participants 19 years of age or older admitted to burn unit within 96 hours of injury with a burn of 20% or more; need for burn excision and grafting was anticipated • Liberal group: n = 177; M/F = 139/38; median age 41 (IQR, 30 to 55)

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Palmieri 2017 *(Continued)*

	• Restrictive group: n = 168; M/F = 134/34; median age 41 (IQR, 27 to 55)
Interventions	• Liberal group: transfused when Hb was < 10 g/dL; maintained Hb between 10 g/dL and 11 g/dL • Restrictive group: transfused when Hb was < 7 g/dL; maintained Hb between 7 g/dL and 8 g/dL Transfusion was administered 1 unit at a time
Outcomes	**Primary outcome:** bloodstream infection **Secondary outcomes included:** mortality, number of infectious episodes (urinary tract infections, pneumonia, wound infection), burn ICU length of stay, hospital length of stay, duration of mechanical ventilation, organ dysfunction (MODS), time to 90% burn wound healing (defined as 7 days after last excision and grafting procedure)
Notes	**Trial registration (prospective):** NCT01079247 **Trial funding:** "this study was supported by the American Burn Association and funded by USAMRMC Award W81XWH-08-1-0760 with support from the National Center for Research Resources, National Institutes of Health, through grant UL1 RR024146, the National Center for Advancing Translational Sciences, National Institutes of Health, through grant TR 000002, and the National Center for Advancing Translational Sciences, National Institutes of Health through grant UL1 TR001860" (Palmieri 2017 p 1) **COI statement by investigators:** "Dr. Holmes: equity positions in Abbott Labs, AbbVie, and Permederm Inc. Dr. Tredget: contract research, Scar X, KLOX Therapeutics, and Exciton (ExSALT), collaborative research British Canadian BioSciences Corp (novel antifibrotic agent). The remaining authors report no conflicts of interest" (Palmieri 2017 p 1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not specified but adaptive random allocation procedure used to balance groups with respect to screening prognostic variables using a "biased coin" procedure, which creates low risk of bias
Allocation concealment (selection bias)	Low risk	Not specified but adaptive random allocation procedure used to balance groups with respect to screening prognostic variables using a "biased coin" procedure, which creates low risk of bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Blinding of participants and personnel was not addressed
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Blinding of outcome assessment was not addressed
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	29 (8%) patients withdrew
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT01079247). No reporting bias was apparent

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Palmieri 2017 *(Continued)*

Other bias	Low risk	No other biases were apparent

Parker 2013

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site trial **Setting:** general hospital, Peterborough, UK **Recruitment:** not stated in paper; ISRCT states trial ran from 2002 to 2012 **Maximum follow-up:** 12 months
Participants	200 participants 60 years of age or older with hip fracture whose postoperative Hb on postoperative day 1 or 2 was 8.0 g/dL to 9.5 g/dL • 'Transfusion' group: n = 100; mean age (range) = 84.4 (60 to 104) years • 'No transfusion' group (aka symptomatic): n = 100; mean age (range) = 84.2 (60 to 97) years
Interventions	Participants had postoperative Hb in a prescribed range (8.0 g/dL to 9.5 g/dL) For the purposes of this review, the trial author's definitions of 'transfusion' group = liberal, and 'no transfusion' or 'symptomatic' = restrictive • Liberal group: transfusion administered immediately and continued until Hb was maintained at > 10.0 g/dL • Restrictive group: no transfusion administered unless prespecified symptoms appeared, specifically, recurrent vasovagal episodes on mobilisation, chest pain of cardiac origin, congestive cardiac failure, unexplained tachycardia, hypotension or dyspnoea thought to be due to anaemia, decreased urine output unresponsive to fluid replacement, or other symptoms felt appropriate by the medical staff
Outcomes	Mobility, mental agility, physical status using American Society of Anesthesiologists grades
Notes	**Trial registration (not prospective):** ISRCTN61328173 **Trial funding:** "there was no external funding for this study" (Parker 2013 p 1918) **COI statement by investigators:** "the author does not have any conflict of interest with this article" (Parker 2013 p 1918)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was undertaken using numbered, sealed, opaque envelopes that were prepared before the start of the study"
Allocation concealment (selection bias)	Low risk	Trial used opaque numbered envelopes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'

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Parker 2013 *(Continued)*

		Blinding of participants and personnel was not addressed
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Blinding of outcome assessment was not addressed
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Blinding of outcome assessor was not addressed for mobility
Incomplete outcome data (attrition bias) All outcomes	High risk	Mobility score was missing for 94 of 200 participants
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent; however, trial was retrospectively registered (ISRCTN61328173), and in the absence of a protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases were apparent

Prick 2014

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre trial **Setting:** 37 university and general hospitals in the Netherlands **Recruitment:** May 2004 to February 2011 **Maximum follow-up:** 6 weeks
Participants	Participants with postpartum haemorrhage (blood loss ≥1000 mL or decrease in Hb ≥1.9 g/dL, or both) and Hb between 4.8 g/dL and 7.9 g/dL 12 to 24 hours after delivery 521 randomised, 2 excluded from analysis (included 3 days postpartum), 519 remained • Liberal group: n = 258; mean age (SD) = 30.7 (5.0) years • Non-intervention group: n = 261; mean age (SD) = 30.9 (5.3) years 40 "did not comply" with allocated intervention
Interventions	• Liberal group: participants received at least 1 unit of RBCs; trialists aimed to reach Hb ≥ 8.9 g/dL • Restrictive group: participants received no transfusion unless they had severe symptoms
Outcomes	**Primary outcome:** physical fatigue 3 days postpartum using the Multidimensional Fatigue Inventory Scale
Notes	**Trial title:** Well-Being of Obstetric Patients on Minimal Blood Transfusions (WOMB) **Trial registration:** NCT00335023 **Trial funding:** Landsteiner Foundation for Blood Transfusion Research (file number 0904) and Stichting Vrienden van de Bloedtransfusie (file number 1201-995). "The funders had no role in study design, data collection and analysis, data interpretation, decision to publish or preparation of the manuscript" (Prick 2014 p 1013)

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Prick 2014 *(Continued)*

COI statement by investigators: "all authors confirm no conflicts of interest with regards to the data reported" (Prick 2014 p 1013)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	After informed consent, women were randomly allocated in a 1:1 ratio to receive RBC transfusion or no intervention, using a web-based application for block randomisation with a variable block size of 2 to 8. Randomisation was stratified for mode of delivery and participating hospital
Allocation concealment (selection bias)	Low risk	Trial used a web-based application with block randomisation of variable block size
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Participants were not blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Primary outcome was based on a questionnaire for fatigue; it is unclear how assessors were blinded and participants were not
Incomplete outcome data (attrition bias) All outcomes	High risk	521 randomised, 2 excluded from analysis (included 3 days postpartum), 519 remained. 40 "did not comply" with allocated intervention (imbalanced numbers: 33 in 'non intervention' arm; 7 in RBC arm) 20% of data for the primary outcome was missing. Health-related quality of life data were available for 78% and 81% of patients in the 2 arms
Selective reporting (reporting bias)	Low risk	NCT00335023l. Trial was preregistered and mortality was never planned to be an outcome, which was clinically appropriate for this population
Other bias	Low risk	No other biases were apparent. 11% of women in the non-intervention (restrictive) arm received transfusions

Robitaille 2013

Study characteristics

Methods	**Design:** RCT, intended to be multicentre trial **Setting:** 1 institution (not identified), Canada **Recruitment:** June 2009 **Maximum follow-up:** intended to be 5 years (overall survival)
Participants	Children aged 1 to 18 years who were undergoing an allogeneic BMT for malignant or benign disease (except sickle cell disease) were eligible Recruitment target was 62; enrolment was 6

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Robitaille 2013 *(Continued)*

	3 - liberal threshold trigger transfusion strategy 3 - restrictive threshold trigger transfusion strategy
Interventions	• Liberal group: transfusion administered at threshold of 12.0 g/dL • Restrictive group: transfusion administered at threshold of 7.0 g/dL
Outcomes	Time to neutrophil engraftment, time to platelet engraftment, transfusions given, length of stay, immune reconstitution, mortality/overall survival (2 to 5 years), graft vs host disease, relapse, chimerism
Notes	Trial closed early due to an excess of cases of veno-occlusive disease in 3 out of 6 cases, all in the intervention (liberal) arm **Trial registration:** NCT00937053 **Trial funding:** Fonds de laRecherche en Santé du Québec (grants 9967 and 24460) **COI statement by investigators:** "the authors declare no conflict of interest to report"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization of patients was done on the first day of their conditioning regimen using a web-based randomization system" (Robitaille 2013 p 469)
Allocation concealment (selection bias)	Low risk	As above - no further information supplied
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low' Primary outcome of veno-occlusive diease is also a hard outcome
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data presented for small cohort
Selective reporting (reporting bias)	Low risk	All data presented for small cohort; 1 death at 6 months in experimental arm. Small sample size rendered many predefined outcomes inappropriate
Other bias	Low risk	Trial closed early due to an excess of cases of veno-occlusive disease in 3 out of 6 cases, all in the intervention (liberal) arm Overall considered at low risk of bias based on limited data available for analysis within this review

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Shehata 2012

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, open-label, single-site pilot trial **Setting:** university teaching hospital, Toronto, Canada **Recruitment:** January 2007 to June 2010 **Maximum follow-up:** 30 days
Participants	50 adult participants undergoing cardiac surgery with a CARE score (a score for cardiac surgery participants used to predict morbidity and mortality) of 3 or 4, or participants of advanced age defined as ≥ 80 years • Liberal group: n = 25; mean age (SD) = 68.8 (9.2) years • Restrictive group: n = 25; mean age (SD) = 67.2 (11.2) years
Interventions	• Liberal group: received transfusion if Hb was ≤ 9.5 g/dL during CPB and < 10 g/dL after CPB • Restrictive group: received transfusion if Hb was ≤ 7.0 g/dL during CPB and ≤ 7.5 g/dL after CPB
Outcomes	**Primary outcome:** enrolment rate and overall adherence to transfusion strategies (pilot study). Clinical outcomes were assessed
Notes	**Trial title:** Transfusion Triggers in Cardiac Surgery **Trial registration (not prospective; record posted 6 months after trial start):** NCT00470444 **Trial funding:** this trial was supported by Canadian Blood Services SPF XT00070. Canadian Blood Services as a funding agency had no role in the design and conduct of the trial **COI statement by investigators:** "the authors declare that they have no conflicts of interest relevant to the manuscript submitted to TRANSFUSION" (Shehata 2012 p 97)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	An independent statistician generated the allocation sequence
Allocation concealment (selection bias)	Low risk	Opaque sequential sealed envelopes were opened at the start of surgery
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Clinicians and participants were not blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data appeared complete for all 50 participants

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Shehata 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	This pilot trial was registered 6 months after recruitment began. All expected outcomes for a pilot were reported
Other bias	Low risk	No other biases were apparent

So-Osman 2013

Study characteristics	
Methods	**Design:** RCT, parallel, multiple-arm, multiple-site trial **Setting:** 3 hospitals in the Netherlands **Recruitment:** 2001 to 2003 **Maximum follow-up:** 14 days
Participants	603 participants eligible for elective orthopaedic surgery • Liberal group: n = 304; mean age (SD) = 70.7 (9.6) years • Restrictive group: n = 299; mean age (SD) = 70.2 (10.3) years
Interventions	Restrictive transfusion was compared with liberal transfusion regimens, which varied among the 3 hospitals of the original trial - So-Osman 2010 - to such an extent that amongst the 3 hospitals involved, investigators' planned so-called "new" policy (protocol A (restrictive)) " .... was more restrictive than the standard policy (B) for two hospitals and the patients randomised to protocol A were labelled as 'restrictive' and those randomised to protocol B as 'liberal'" However, in the third hospital, "the new transfusion trigger was in fact more liberal than the hospital's existing standard policy. As a consequence, patients randomised to the new policy (protocol A) actually received more RBC transfusions, and this group was now labelled as "liberal", whereas the group randomised to the standard policy (protocol B) was labelled as "restrictive" In brief (and with emphasis added to show the overlap): The protocol intended to be the 'liberal' arm (standard care aka Protocol B) varied between hospitals, thus: • *Hospital 1* - perioperative period (day 0) trigger in range of 8.1 g/dL to 9.7 g/dL (1 to 2 units. Postoperatively (from day 1) if Hb < 9.7 g/dL, 2 RBC units were transfused, independent of age or other risk factors • *Hospital 2* - perioperative period (day 0) target of no transfusion unless Hb **below 6.4 g/dL in low risk (age < 60, ASA class I)**; no transfusion unless < Hb 8.1 g/dL if aged 60 or older and ASA class 1, 2, 3; no transfusion unless < 9.7 g/dL if ASA class IV or serious cardiopulmonary disease. Factors determined treatment from the first postoperative day (day 1), including age and cardiac history, leading to a range for no transfusion until Hb dropped to 7.2 g/dL (young, low risk) and 9.7 g/dL (older, high risk) • *Hospital 3* - perioperative period (day 0) if Hb < 9.7 g/dL and dependent on (expected) blood loss: 2 RBC units were transfused (for all patients). Postoperatively, on day 1, triggers were dependent on risk, but no transfusion until Hb was < 8.1 g/dL in low-risk and 9.7 g/dL in high-risk participants The protocol intended to be the 'restrictive' arm (Protocol A) entailed stratifying participants into 3 risk categories (low, intermediate, and high risk). Risk was determined based on age (> 50 years, 50 to 70 years, > 70 years) and/or any one of 11 conditions (e.g. unstable cardiac ischaemia, heart failure, insulin-dependent diabetes). Within risk categories, triggers differed depending on length of time since surgery (within 4 hours of surgery, or later)

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So-Osman 2013 *(Continued)*

	At the lowest end possible of the range for Protocol A (low-risk patients within 4 hours of surgery), patients received no transfusion if Hb remained **at or above 6.4 g/dL** At the highest end (high-risk patients > 4 hours after surgery), patients received no transfusion if Hb remained at or above 9.7 g/dL Hospital 2 had a more restrictive policy as standard care than that employed in the 'new', supposedly restrictive, Protocol A; therefore for the purposes of analysis, we used data from So-Osman 2013 - in which the arms of the latter trial were reversed and all data were thus appropriate for our comparison
Outcomes	**Primary outcome variable:** RBC use (originally) **Secondary outcomes included:** postoperative complications, quality of life
Notes	Review authors (JC and SS) re-analysed the prior report (So-Osman 2010), comparing restrictive vs liberal transfusion. It should be noted that whilst details of the thresholds applied in this trial are provided in the papers, there were challenges in implementing the protocol at all sites; significant differences between trial arms were not apparent **Trial registration:** none ascertainable **Trial funding:** this trial was fully supported by a grant from the LUMC, Leiden (Doelmatigheidsstudie P01.065) **COI statement by investigators:** "the authors declare no conflicts of interest" (So-Osman 2013 p 6)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"For each stratum, a separate randomization list was created, using blocks of variable length to avoid predictability of the random treatment assignment towards the end of each block. Treatment allocation was random using a uniform distribution for a pregenerated list of sufficient length, based on the maximum expected sample size in each stratum. For each subject to be randomized, a sheet of paper with all relevant stratification and group-allocation information was produced and placed in a sealed opaque envelope. Batches were created according to the stratification factors" (So-Osman 2010 p 57)
Allocation concealment (selection bias)	Low risk	A research nurse opened sealed opaque envelopes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Clinicians caring for participants were aware of allocation status. There was no blinding information on participants
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'. This also relates to transfusion requirements as the trial outcome
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Quality of life measures were reported for an unblinded assessment
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

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So-Osman 2013 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	No trial registration identified
Other bias	Low risk	No other biases were apparent, apart from a slight baseline imbalance (history of COPD more prevalent in restrictive group than in liberal group)

Stanworth 2020

Study characteristics	
Methods	**Design:** RCT, 2-arm parallel, multicentre international feasibility trial **Setting:** 12 sites (UK, Australia, New Zealand) **Recruitment:** 2015 to 2017 **Maximum follow-up:** 3 months
Participants	38 participants: • with diagnosis of MDS based on WHO criteria , ≥ 18 years of age and < 20% blasts on bone marrow aspirate, including non-proliferative CMML and other MDS/MPN overlap diseases; • transfusion dependent, defined as at least 1 red cell transfusion episode per month in the last 8 weeks; and • with life expectancy > 6 months • Liberal group: n = 18; M/F = 14/4; age = 80 (range 69 to 84) years • Restrictive group: n = 20; M/F = 13/7; age = 79 (range 69 to 82) years
Interventions	• Liberal strategy: to maintain Hb between 11.0 g/dL and 12.5 g/dL, transfused 2 units of RBCs when Hb ≤ 10.4 g/dL, and 1 unit of RBCs when Hb was between 10.5 g/dL to 110 g/dL (inclusive) • Restrictive strategy: to maintain Hb between 8.5 g/dL and 10.0 g/dL, transfused 2 units of RBCs when Hb ≤ 7.9 g/dL, and 1 unit of RBCs when Hb was between 8.0 g/dL to 8.5 g/dL (inclusive)
Outcomes	Primary outcomes of this feasibility study, from day 0 to day 84, were: • percentage of pre-transfusion Hb below the target range of assigned red cell transfusion strategy ('compliance to treatment threshold'); and • achievement of ≥ 2.0 g/dL difference between mean pre-transfusion Hb in liberal and restrictive strategy groups For the review primary outcome of mortality, 1 patient was reported to have died (restrictive arm), but the timing was not clear
Notes	**Trial registration:** ISRCTN26088319 **Trial funding:** "funding was provided by grants awarded by NHSBT R&D, the Australian and New Zealand Society of Blood Transfusion (ANZSBT) and the Wellington Division of the New Zealand Cancer Society" (Stanworth 2020 p 289) "The sponsor and funders had no role in the collection, analysis and interpretation of data, the writing of the report or the decision to submit" (p 283) **COI statement by investigators:** "there are no conflicts of interest" (Stanworth 2020 p 289)
Risk of bias	

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Stanworth 2020 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule, stratified block design (blocks of 2 and 4)
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes (prepared from the schedule by an independent member of the clinical trials unit) were opened in sequential order
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Patients were blinded to treatment arm and haemoglobin, but not to transfusions; investigators and clinicians were unblinded to treatment allocation
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Investigators and clinicians were unblinded to treatment allocation, and multiple quality of life measures were reported. Transfusion measures could be altered in response to perceived changes in quality of life measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes were reported; all participants were included in analyses
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered, and all data on all outcomes are reported (ISRCTN26088319)
Other bias	Low risk	Some imbalances between arms were noted, but the trial was small. "Two patients were randomised in error as not red cell transfusion dependent" (Stanworth 2020 p 283); four patients were not transfused despite being a study of transfusion-dependency (p 287)

Tay 2020

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, non-inferiority trial **Setting:** 4 HCT centres, Canada **Recruitment:** March 2011 to February 2016 **Maximum follow-up:** 100 days
Participants	300 participants over 18 years of age undergoing autologous or allogeneic HCT for any haematological malignancy randomised There was one late exclusion • Liberal group: n = 150; M/F = 94/56; age = 56.0 (IQR 48.3 to 62.2) • Restrictive group: n = 149; M/F = 97/52; age = 57.5 (IQR 48.9 to 62.7)
Interventions	• Liberal group: received 2 units of RBCs if Hb fell to < 9.0 g/dL (targeted to maintaining a level of 9.0 g/dL to 11.0 g/dL)

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Tay 2020 *(Continued)*

- Restrictive group: received 2 units of RBCs if Hb fell to < 7.0 g/dL (targeted to maintaining a level of 7.0 g/dL to 9.0 g/dL)

Outcomes	**Primary outcome:** health-related quality of life (HRQOL) measured by FACT-BMT score at day 100
Notes	**Trial registration (prospective):** NCT01237639 **Trial funding:** supported by grants from the Canadian Institute of Health Research and the Canadian Blood Services **COI statement by investigators:** "Jason Tay: **Honoraria:** Celgene, Takeda, Sanofi Canada, Amgen. David S. Allan: **Other Relationship:** Canadian Blood Services. Mohamed Elemary: **Consulting or Advisory Role:** Jazz Pharmaceuticals, Amgen, Roche Canada. Adrienne Fulford: **Honoraria:** Teva Pharmaceutical Industries; **Consulting or Advisory Role:** Amgen. Irwin Walker: **Honoraria:** Jazz Pharmaceuticals; **Consulting or Advisory Role:** Jazz Pharmaceuticals; **Research Funding:** Sanofi Canada;**Travel, Accommodations, Expenses:** Jazz Pharmaceuticals. Anargyros Xenocostas: **Honoraria:** Novartis (Inst), Amgen (Inst), Apobiologix (Inst), Pfizer (Inst); **Research Funding:** Novartis (Inst)" (Tay 2020 p 1474) No other potential conflicts of interest were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Low risk	Secure online electronic randomisation platform was used
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Not possible to blind patients or caregivers
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Health-related outcomes were self-reported and were trial primary outcomes. Patients were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	300 participants were randomised. There was 1 late exclusion in the restrictive group and 2 in each group were lost to full follow-up. 299 participants were included from ITT analysis
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered (NCT01237639). All outcomes appear to be reported
Other bias	Low risk	None was evident. A small difference in storage age at transfusion between the 2 arms was noted. Overall transfusion adherence rate was 95%

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Topley 1956

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-centre trial **Setting:** an 'accident hospital', Birmingham, UK **Recruitment:** not reported. Pre-1957 **Maximum follow-up:** 3 months
Participants	22 trauma participants randomly allocated to 1 of 2 groups • Liberal group: n = 10 • Restrictive group: n = 12 NB: no demographic data were reported
Interventions	• Liberal group: aim was to achieve 100% or more of [normal] RBC volume at the end of resuscitation • Restrictive group: an attempt was made to leave RBC volume at the end of resuscitation at 70% to 80% of normal
Outcomes	Blood usage (units), blood loss, wound healing, elevated temperature, number of participants transfused, Hb. Deaths were reported, but timing and transfusion strategy were not provided
Notes	**Trial registration:** none ascertainable **Trial funding:** none reported **COI statement by investigators:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Use of random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Trial used sealed envelopes. When participants were considered eligible for the trial, they were placed in a severity grade and an envelope was opened to decide which transfusion schedule was to be used
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	High risk	Trial did not report in which group the deaths occurred; therefore we classified this as high risk of bias
Selective reporting (reporting bias)	High risk	Trial did not report in which group the deaths occurred; therefore we classified this as high risk of bias

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Topley 1956 *(Continued)*

Other bias	Low risk	No other biases were apparent

Villanueva 2013

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, single-site, phase 4 trial **Setting:** large general hospital, Barcelona, Spain **Recruitment:** June 2003 to December 2009 **Maximum follow-up:** 45 days
Participants	Participants > 18 years of age who had haematemesis or melena, or both (due to upper GI bleeding) 921 randomised • Liberal group: n = 460; mean age (SD) = 64 (16) years. After 15 withdrawals, 445 were included in analysis • Restrictive group: n = 461; mean age (SD) = 66 (15) years. After 17 withdrawals, 444 were included in analysis
Interventions	• Liberal group: transfused when Hb < 9 g/dL • Restrictive group: transfused when Hb as < 7 g/dL In both groups, 1 unit of RBCs was transfused initially
Outcomes	**Primary outcome:** death at 45 days **Secondary outcomes included:** rate of further bleeding, rate of in-hospital complications
Notes	**Trial registration** (December 2006 to not prospective): NCT00414713 **Trial funding:** Fundació Investigació Sant Pau **COI statement by investigators:** "Dr. Guarner reports receiving consulting fees from Sequana Medical. No other potential conflict of interest relevant to this article was reported" (Villanueva 2013 p 20)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence generation was computer generated
Allocation concealment (selection bias)	Low risk	Trial used sealed consecutively numbered, opaque envelopes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Clinicians and participants were not blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'

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Villanueva 2013 *(Continued)*

		Mortality was the primary trial outcome. Assessors of other outcomes were not documented to be blinded
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 15 withdrawals from the liberal arm (of 460 participants) and 17 withdrawals from the restrictive arm (of 461 participants)
Selective reporting (reporting bias)	Unclear risk	Trial was registered post hoc (3 years after recruitment began). The primary outcome changed from death at 30 days (December 2006) to death at 45 days (November 2007) (all data were obtained from primary author of trial report by JC)
Other bias	Low risk	No other biases were apparent

Walsh 2013

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre, pilot study **Setting:** 6 ICUs in university teaching and general hospitals (UK) **Recruitment:** August 2009 to December 2010 **Maximum follow-up:** 6 months
Participants	100 ICU participants aged ≥ 55 years, Hb < 9 g/dL, mechanical ventilation for ≥ 96 hours, who were expected to require ≥ 24 hours of further mechanical ventilation when assessed • Liberal: n = 49; mean age (range) = 68 (55 to 83) years • Restrictive: n = 51; mean age (range) = 67 (56 to 80) years
Interventions	• Liberal group: received transfusion when Hb ≤ 9.0 g/dL, with target Hb of 9.1 g/dL to 11.0 g/dL • Restrictive group: received transfusion when Hb ≤ 7.0g/dL, with target Hb of 7.1 g/dL to 9.0 g/dL
Outcomes	**Primary feasibility outcome:** difference in mean Hb among groups. Clinical outcomes were assessed, including SF-12 (with physical function scale)
Notes	**Trial name:** Restrictive versus Liberal Transfusion Strategies for Older Mechanically Ventilated Critically Ill Patients (RELIEVE) **Trial registration (prospective):** NCT00944112 **Trial funding:** supported, in part, by the Chief Scientists Office, Scotland (CZB/4/698); the Scottish National Blood Transfusion Service, the NHS Lothian Academic Health Science Centre; and the Transfusion Medicine Education and Research Foundation **COI statement by investigators:** no statement of interest reported in the paper

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Walsh 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Minimisation by centre and the presence of IHD, including a random element, was used" (Walsh 2013 p 2355)
Allocation concealment (selection bias)	Low risk	Trial used telephone randomisation
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Clinicians were not blinded. Most surviving participants stated that they were unaware of group allocation at 180 days (restrictive group: 67%; liberal group: 78%); 23% of participants in the restrictive group and 9% in the liberal group correctly stated their treatment group
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Researchers concealed from group allocation collected questionnaire-based measures at 60 and 180 days post randomisation. Clinical outcomes were not documented to have been done blindly; however, investigators did ask surviving patients at 180 days which group they thought they had been allocated to
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were rare at long-term follow-up At 60 days, of surviving participants in the restrictive group (37/51), there were 29/37 complete RMIs (Rivermead Mobility Index) and 23/37 completed SF-12s. At 180 days, of surviving participants in this group (33), there were 29 complete RMIs and 28 SF-12s and 29 HE questionnaires At 60 days, of surviving participants in the restrictive group (27/49), there were 26/27 complete RMIs and 23/27 completed SFIs. At 180 days, of surviving participants in this group (22), there were 21 complete RMIs and 21 SF-12s and 20 HE questionnaires
Selective reporting (reporting bias)	Low risk	Trial registration was prospective. No reporting bias was apparent
Other bias	Low risk	No other biases were apparent

Webert 2008

Study characteristics	
Methods	**Design:** RCT, parallel 2-arm, multicentre feasibility study **Setting:** 4 tertiary haematology centres (Canada) **Recruitment:** March 2003 to October 2004 **Maximum follow-up:** 30 days
Participants	60 adult participants with acute leukaemia were randomly allocated to 1 of 2 groups:

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Webert 2008 *(Continued)*

	• Liberal group: n = 31; M/F = 14/17; mean (SD) age = 45.3 (16.8) years • Restrictive group: n = 29; M/F = 1811; mean (SD) age = 50.8 (15.3) years
Interventions	• Liberal group: transfused with 2 units of RBCs when Hb fell to < 12.0 g/dL • Restrictive group: transfused with 2 units of RBCs when Hb dropped to < 8.0 g/dL, with target range of 8.5 g/dL to 9.5 g/dL
Outcomes	Transfusions, bleeding risk, 30-day mortality provided by trial authors
Notes	**Trial registration:** none ascertainable **Trial funding:** "This study was funded by a grant from Canadian Blood Services and a CIHR Canada Research Chair. KEW was supported by a Canadian Blood Services/Novo Nordisk Research Fellowship in Hemostasis. RJC is a Canada Research Chair" (Webert 2008 p 81) **COI statement by investigators:** no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was computer generated
Allocation concealment (selection bias)	Low risk	Allocation was Internet based and central
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Participants and clinicians were not blinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	Low risk	No data from subjective outcomes (e.g. function)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No data were missing
Selective reporting (reporting bias)	Unclear risk	No reporting bias was apparent, but in the absence of prospective registration or a trial protocol, assessment must remain 'unclear'
Other bias	Low risk	No other biases were apparent

Yakymenko 2018

Study characteristics

Methods	**Design:** RCT, parallel 2-arm, open-label, single-site, phase 2 (feasibility) trial **Setting:** oncology department, university teaching hospital, Copenhagen, Denmark

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Yakymenko 2018 *(Continued)*

	Recruitment: March 2010 to March 2013 **Maximum follow-up:** follow-up during chemotherapy cycles
Participants	133 participants undergoing chemotherapy at the Department of Oncology • Liberal group: n = 68; M/F = 29/39; mean (SD) age = 65 (9.9) years • Restrictive group: n = 65; M/F =35/30; mean (SD) age = 65 (9.7) years
Interventions	• Liberal group: transfused when Hb < 11.5 g/dL in women and < 13.1 g/dL in men • Restrictive group: transfused when Hb < 9.7 g/dL
Outcomes	**Primary objective (authors stated):** to establish correlation between quality of life and Hb **Secondary objectives:** to compare relief of symptoms and improvement in quality of life between randomisation arms, to provide data to plan a larger randomised trial (e.g. safety, completion rate, clinician compliance with protocol) Outcome data were not presented by transfusion group
Notes	**Trial registration:** NCT 01116479 (submitted in April 2010; trial had already begun in March 2010, but registration was deemed prospective) **Trial funding:** not reported **COI statement by investigators:** "the authors have no competing interests" (Yakymenko 2018 p 214)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"When included, patients were randomly assigned to one of two transfusion trigger levels through a computer programme" (Yakymenko 2018 p 209)
Allocation concealment (selection bias)	Unclear risk	As above - no information other than - "When included, patients were randomly assigned to one of two transfusion trigger levels through a computer programme" (Yakymenko 2018 p 209)
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of personnel for this intervention is not feasible, but in our view, for objective outcomes such as mortality (the primary outcome used within this review), we graded risk of bias as 'low' Unblinded
Blinding of outcome assessment (detection bias) Objective measures	Low risk	Blinding of mortality (the primary outcome used within this review) is not relevant, and we graded risk of bias as 'low'
Blinding of outcome assessment (detection bias) Subjective measures	High risk	Self-reported questionnaires were applied in an unblinded trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 65 participants in the restrictive arm, 28 received RBC transfusion. Reasons for 37 who did not included termination of chemotherapy (20); patient request (1); death (1); unknown (2); 'end of study period' (13). 5 questionnaires from the remaining 28 were missing, so 23/28 questionnaires were analysed Of 68 participants in the liberal arm, 58 received RBC transfusion. 10 did not, because of termination of chemotherapy (3); patient request (4); death (2);

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Yakymenko 2018 *(Continued)*

		'end of study period' (1). 12 questionnaires of the remaining 28 were missing, so 46/58 questionnaires were analysed
Selective reporting (reporting bias)	Low risk	Paper does not appear to be explicit about timing of deaths (3); however, the questionnaires appear to have been administered within 7 days of any transfusions delivered, so in our view (since deaths are reported as reasons for not getting questionnaires filled in), these deaths must have occurred within a 7-day period Trial registration close to prospective; investigators submitted registration on 28 April for a trial that began in March
Other bias	Low risk	Trial was stopped early due to 'low accrual'. Investigators aimed to recruit 180 participants

Abbreviations

ACS: acute coronary syndrome
ARDS: acute respiratory distress syndrome
ASA: American Society of Anaestheologists
BMT: bone marrow transplant
CABG: coronary artery bypass grafting
CARE: Cardiac Anesthesia Risk Evaluation
CMML: chronic myelomonocytic leukaemia
COPD: chronic obstructive pulmonary disease
CPB: cardiopulmonary bypass
DSMB: Data Safety Monitoring Board
ECG: electrocardiogram
GI: gastrointestinal
Hb: haemoglobin concentration
Hct: haematocrit
HCT: hematopoietic cell transplantation
HE: health economics
ICU: intensive care unit
IHD: ischaemic heart disease
IQR: interquartile range
ITT: intention-to-treat
MACE: major adverse cardiac events
MDS: myelodysplastic syndrome
M/F: male/female
MODS: multiple organ dysfunction syndrome
MPN: myeloproliferative neoplasm
PAB: preoperatively donated autologous blood
PCI: percutaneous coronary intervention
PI: principal investigator
PLTs: platelets
QOL: quality of life
RBCs: red blood cells
RCT: randomised controlled trial
RMI: Rivermead Mobility Index
ROTEM: rotational thromboelastometry
SB: Sengstaken-Blakemore
SD: standard deviation
SF-12: Short Form Health Survey
TKA: total knee arthroplasty
VA: US Department of Veterans Affairs
WHO: World Health Organization

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

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Study	Reason for exclusion
Atilla 2017	RCT. Ineligible intervention (haemoglobin content-based vs standard (unit-based) transfusion policy, rather than threshold))
Baron-Stefaniak 2019	RCT. Ineligible intervention; not haemoglobin threshold
Cholette 2017	RCT. Ineligible participants (infants (cardiac))
de Bruin 2019	Ineligible design. Survey amongst ICU physicians reviewing transfusion practices
Elshinawy 2020	RCT. Ineligible intervention; not haemoglobin threshold
Fogagnolo 2020	Ineligible design. Prospective observational study
Fortune 1987	RCT (reported only in an abstract) appeared to measure only oxygen utilisation. Investigators planned no clinical outcomes of interest
Franz 2020	RCT. Ineligible participants (neonates (low birth weight))
Haensig 2019	RCT. Ineligible intervention (not red cell transfusion but thrombelastometry guided blood-component therapy)
Hamm 2020	RCT. Ineligible intervention (trial assessed effects of single-unit vs multiple-unit transfusion, rather than threshold)
Jain 2019	RCT. Ineligible intervention (trial assessed effects of known haemoglobin content of packed red blood cell units vs standard transfusion practice in thalassaemia major)
Kirpalani 2020	RCT. Ineligible participants: neonates
Koster 2016	Ineligible design. Ineligible intervention. This single-centred retrospective cohort study looked at coronary artery bypass patients who received either 1 to 2 or no units of blood
Kumar 2019	RCT. Ineligible intervention (not red cell transfusion but thrombelastometry guided blood-component therapy)
Leal-Noval 2017	RCT. Ineligible intervention (trial assessed effects of using a transcranial oxygen saturation threshold, as measured by near-infrared spectroscopy, in neurocritically ill patients)
Osawa 2016	RCT. Ineligible intervention (trial assessed effects of cardiac output-guided haemodynamic therapy algorithm (goal-directed therapy group) or usual care)
Robertson 2014	RCT. Ineligible intervention/comparator. The trial employed a 2 × 2 factorial design in which participants received erythropoietin or transfusion at different thresholds. We were unable to isolate the effects of transfusion from erythropoietin
Vichinsky 1995	RCT. Ineligible intervention. The transfusion trigger was based on the level of sickle haemoglobin, not the haemoglobin or haematocrit level
Voorn 2017	RCT. Ineligible intervention (trial focused on educating clinicians to cease to use preoperative erythropoietin and perioperative autologous blood salvage, rather than transfusion thresholds)
Yamada 2020	Ineligible design. Survey of details on antigen-positive RBC transfusions (826 cases from 45 institutions)
Zygun 2009	RCT. Eligible intervention. Ineligible focus - this trial measured oxygen utilisation and planned no clinical outcomes of interest

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Abbreviations
ICU: intensive care unit
RBCs: red blood cells
RCT: randomised controlled trial

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

IRCT20190209042660N1

Methods	RCT (Iran)
Participants	Patients > 18 years of age with > 20% body surface thermal burns
Interventions	Intervention: blood transfusion when patient's blood haemoglobin is below 8 mg [sic]/dL Control group: blood transfusion when patient's blood haemoglobin is below 10 mg [sic]/dL
Outcomes	Total number of transfused blood bags, mortality during hospitalisation, inpatient morbidity (including wound infection; positive blood culture; sepsis; cardiac, pulmonary, neurological, and compartment syndrome); total episodes of infection (each infection); duration of time in hospital
Notes	Trial registration: IRCT20190209042660N1 Not prospectively registered. Trial began recruitment in 2018. Ethics approval reported as 2019. Trial registered 2020

ISRCTN26088319

Methods	RCT (UK, Australia, New Zealand)
Participants	Participants with MDS, transfusion dependent, life expectancy > 6 months
Interventions	Liberal protocol: to maintain haemoglobin concentration Restrictive protocol: to maintain haemoglobin level between 8.5 g/dL and 10 g/dL
Outcomes	Percentage of compliance of pre-transfusion haemoglobin levels with achievement of at least 2 g/dL difference between liberal and restrictive transfusion
Notes	Trial registration (prospective): ISRCTN26088319

Maitland 2019

Methods	RCT (multicentre; Uganda, Malawi)
Participants	Children aged 2 months to 12 years (median 37 months) with haemoglobin level < 6 g/dL and severity features
Interventions	Complex. The main intervention involved receipt of immediate blood transfusion with 20 mL/kg or 30 mL/kg. Three other randomised analyses also investigated: • immediate compared with no immediate transfusion; • provision of postdischarge micronutrients; and • postdischarge prophylaxis with trimethoprim–sulfamethoxazole
Outcomes	**Primary outcome:** 28-day mortality

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Maitland 2019 *(Continued)*

Notes	Trial registration (prospective): ISRCTN84086586

Morton 2020

Methods	RCT (feasibility) (UK)
Participants	Adults with acute myeloid leukaemia
Interventions	Red cell transfusions
Outcomes	Feasibility, quality of life
Notes	Trial registration (prospective): ISRCTN96390716

NCT02099669

Methods	RCT (feasibility) (Canada)
Participants	All participants with MDS ≥ 18 years of age, transfusion dependent: at least 1 transfusion per month in the last 8 weeks, haemoglobin < 10 g/dL
Interventions	Liberal transfusion strategy: to maintain Hb between 11 g/dL and 12 g/dL Restrictive transfusion strategy: to maintain Hb between 8.5 g/dL and 10 g/dL
Outcomes	Percentage compliance
Notes	Trial registration (prospective): NCT02099669

Abbreviations
Hb: haemoglobin concentration
MDS: myelodysplastic syndrome
RCT: randomised controlled trial

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

ACTRN12619001053112

Study name	REDDS2: Red Cell Transfusion Schedule in Melodysplastic Syndrome
Methods	RCT (feasibility)
Participants	Patients with transfusion-dependent MDS Estimated enrolment: 30
Interventions	Red cell transfusions: liberal weekly policy (Hb < 11 g/dL) vs standard policy
Outcomes	Feasibility
Starting date	2020

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ACTRN12619001053112 *(Continued)*

Contact information	Allisson Mo; allison.mo1@monash.edu
Notes	Trial registration (prospective): ACTRN12619001053112 Universal trial identifier: U11112316575 (UTN) Funding: Australian & New Zealand Society of Blood Transfusion (ANZSBT); National Blood Authority; Monash Haematology Research fund (Australia)

Hayakawa 2020

Study name	Restrictive Transfusion Strategy for Critically Injured Patients (RESTRIC)
Methods	RCT (multicentre; cluster)
Participants	Severe trauma Estimated enrolment: 22 hospitals; n = 400
Interventions	Transfusions to target Hb 7 g/dL to 9 g/dL vs 10 g/dL to 12 g/dL
Outcomes	Survival at 28 days
Starting date	2019
Contact information	Mineji Hayakawa; mineji@dream.com
Notes	Trial registration (prospective): UMIN000034405 Funding: supported in part by research grants from The General Insurance Association of Japan and The Marumo Emergency Medical Research Promotion Fund (Japan)

ISRCTN17438123

Study name	RePAST: Red cell transfusion in Paediatric Allogeneic HSCT - a feasibility randomised controlled trial comparing restrictive versus liberal RBC transfusion strategies in children undergoing allogeneic HSCT
Methods	RCT (feasibility)
Participants	Children (aged 1 to 17 years) undergoing allogeneic HSCT Estimated enrolment: 34
Interventions	Restrictive (Hb < 6.5 g/dL) vs liberal red cell transfusion (Hb < 8.0 g/dL) policies
Outcomes	Feasibility outcomes
Starting date	2019
Contact information	Val Hopkins; valerie.hopkins@nhsbt.nhs.uk
Notes	Trial registration (prospective): ISRCTN17438123

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ISRCTN17438123 *(Continued)*

	Funding: NHSBT Trust Fund Grant (UK)

Meybohm 2019

Study name	Liberal Transfusion Strategy to Prevent Mortality and Anaemia-associated, Ischaemic Events in Elderly NOn-cardiac Surgical Patients - the LIBERAL Trial
Methods	RCT (multicentre)
Participants	Elderly (≥ 70 years) surgical patients for non-cardiac surgery Estimated enrolment: 2470
Interventions	Liberal vs restrictive transfusions (9 g/dL vs 7.5 g/dL)
Outcomes	All-cause mortality, myocardial infarction, stroke, kidney injury
Starting date	2018
Contact information	Patrick Meybohm; patrick.meybohm@kgu.de
Notes	Trial registration (prospective): NCT03369210 Funding: support from the German Research Foundation (Deutsche Forschungsgemeinschaft; grant no. ME 3559/3–1) (Germany)

NCT02981407

Study name	Myocardial Ischemia and Transfusion (MINT)
Methods	RCT (multicentre; international)
Participants	Adults with STEMI or non-STEMI consistent with the 3rd Universal Definition of Myocardial Infarction criteria (Thygesen 2012), as assessed on admission or during the index hospitalisation Estimated enrolment: 3500 (including participants enrolled in earlier pilot conducted in Canada (NCT0248335)). The pilot (intended to recruit 60 participants) is complete; participants' results will be published when the main trial reports, not separately
Interventions	Red cell transfusion liberal (10 g/dL) vs restrictive (7 g/dL)
Outcomes	Mortality and non-fatal myocardial reinfarction
Starting date	2017
Contact information	Jeff Carson; jeffrey.carson@rutgers.edu; Helaine Noveck; Helaine.Noveck@Rutgers.edu
Notes	Trial registration (prospective): NCT02981407 Funding: NLHBI (USA)

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NCT03229941

Study name	Transfusion Trigger after Operations in High Cardiac Risk Patients (TOP)
Methods	RCT (multicentre)
Participants	The trial will include people having: • open (non-endovascular) PAD-related operations; and • selected major vascular and general operations with a prior history of PAD or IHD Estimated enrolment: 3070
Interventions	• Liberal group: transfusion trigger at Hb < 10 g/dL • Restrictive group: transfusion trigger at Hb < 7 g/dL
Outcomes	A composite endpoint of all-cause post-randomisation mortality, myocardial infarction, coronary revascularization, acute renal failure, or post-randomisation ischaemic stroke up to 90 days after randomisation
Starting date	2018
Contact information	Panagiotis Kougias; panagiotis.kougias@va.gov Sherene Sharath; sherene,sharath@va.gov
Notes	Trial registration (prospective): NCT03229941 Sponsor: Veterans Affairs Office of Research and Development (USA)

NCT03260478

Study name	HEMOglobin Transfusion Threshold in Traumatic Brain Injury OptimizatioN: The HEMOTION Trial (HEMOTION)
Methods	RCT (multicentre)
Participants	Adults with acute moderate or severe traumatic brain injury Estimated enrolment: 712
Interventions	Liberal group: RBC transfusion if Hb ≤ 10 g/dL Restrictive group: RBC transfusion if Hb < 7 g/dL
Outcomes	Extended Glasgow Outcome Scale (GOSe) (time frame: 6 months)
Starting date	2017
Contact information	Lucy Clayton; hemotion@crchudequebec.ulaval.ca Alexis Turgeon; alexis.turgeon@fmed.ulaval.ca
Notes	Trial registration (prospective): NCT03260478 Funding: CIHR (Canada)

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NCT03309579

Study name	Aneurysmal SubArachnoid Hemorrhage - red blood cell transfusion and outcome (SAHaRA)
Methods	RCT (multicentre; international; pragmatic)
Participants	Adults with aneurysmal subarachnoid haemorrhage Estimated enrolment: 740 (including participants enrolled in earlier pilot (NCT02483351)) NCT02483351 is now complete; participants' results will be published when the main trial reports, not separately
Interventions	Liberal vs restrictive threshold (10 g/dL vs 8 g/dL)
Outcomes	Primary outcome: modified Rankin scale (for measuring functional outcome in stroke) Mortality will be reported at 12 months
Starting date	2018
Contact information	Shane English; senglish@toh.ca
Notes	Trial registration (prospective): NCT03309579 Funding: supported by a Transfusion Science research grant awarded by a Canadian Blood Services and Health Canada in partnership with CIHR Institute of Circulatory and Respiratory Health (Canada)

NCT03871244

Study name	Pilot Optimising Transfusion Thresholds in Critically Ill Children with Anaemia (pOpTTICCA)
Methods	RCT (feasibility for a large pragmatic trial)
Participants	Children admitted to paediatric ICU Estimated enrolment: 120
Interventions	Red cell transfusion: restrictive (Hb < 7 g/dL) vs standard of care
Outcomes	Feasibility measures including recruitment
Starting date	2019
Contact information	Jacques Lacroix; jacques.lacroix.hsj@ssss.gouv.qc.ca
Notes	Trial registration (prospective): NCT03871244 Funding: CIHR (Canada)

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NCT04506125

Study name	Liberal versus Restrictive Transfusion Threshold in High-risk Oncologic Surgery: a multicenter, randomised, controlled, pilot study
Methods	RCT (multicentre, pilot)
Participants	Cancer surgery Estimated enrolment: 30
Interventions	Liberal arm: Hb 9.5 g/dL threshold for transfusion Restrictive arm: Hb 7.5 g/dL threshold for transfusion
Outcomes	Listed as: method of the pilot study, epidemiological data of the pilot study
Starting date	2021
Contact information	Cécile Aubron; cecile.aubron@chu-brest.fr Xavier Chapalain; xavier.chapalain@chu-brest.fr
Notes	Trial registration (prospective): NCT04506125 Funding: none specified. Sponsor is University Hospital, Brest (France)

NCT04591574

Study name	Anaemia Management with Red Blood Cell Transfusion to Improve Post-Intensive Care Disability: a randomised controlled trial (the ABC Post-intensive Care Trial)
Methods	RCT (multicentre - acute hospitals throughout the UK)
Participants	Patients > 16 years old considered ready for ICU discharge with Hb < 9.4 g/dL Estimated enrolment: 305
Interventions	Liberal group: transfusion at Hb 10 g/dL threshold Restrictive group: transfusion at Hb 7.0 g/dL threshold
Outcomes	Health-related quality of life (SF-36)
Starting date	2020
Contact information	Timothy Walsh; ABC.Trial@ed.ac.uk
Notes	Trial registration (prospective): NCT04591574 Funding: Moulton Grant (UK)

NCT04754022

Study name	TRICSIV: an international, multicentre, randomised controlled trial to assess transfusion thresholds in younger patients undergoing cardiac surgery

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NCT04754022 *(Continued)*

Methods	RCT (multicentre)
Participants	Adults (≥ 18 and ≤ 65 years of age) undergoing planned cardiac surgery Estimated enrolment: 1440
Interventions	Liberal group: transfusion at Hb < 9.5 g/dL threshold Restrictive group: transfusion at Hb < 7.5 g/dL threshold
Outcomes	Composite score of any 1 of the following events occurring 6 months after cardiac surgery: all-cause mortality, myocardial infarction, new-onset renal failure requiring dialysis, new focal neurological deficit (stroke)
Starting date	2021
Contact information	David Mazer; david.mazer@unityhealth.to Nadine Shehata; Mount Sinai Hospital, NY, USA
Notes	Trial registration (prospective): NCT04754022 Funding: not specified, but sponsor/collaborator is listed as Unity Health Toronto (Canada)

NIHR 130875

Study name	The impact of REstrictive versus LIberal Transfusion strategy on cardiac injury and death in patients undergoing surgery for Hip Fracture (RESULT-Hip)
Methods	RCT
Participants	Adults aged 60 years or older with hip fracture who become anaemic (< Hb 9.0 g/dL) during the 7 days following surgery Estimated enrolment: 1964
Interventions	Liberal group: transfusion threshold of Hb 9.0 g/dL (target Hb 9.0 g/dL to 11.0 g/dL) for duration of acute hospital stay Restrictive group: transfusion threshold of Hb 7.5 g/dL (target Hb 7.5 g/dL to 9.0 g/dL) for duration of acute hospital stay
Outcomes	**Primary outcome:** death or MACE within 30 days of surgery. MACE will be defined as any combination of the following: death, myocardial Infarction, new arrhythmia, cardiac or respiratory arrest, cardiogenic pulmonary oedema
Starting date	2022
Contact information	Michael Gillies; michael.gillies@ed.ac.uk
Notes	Funding: National Institute for Health Research (NIHR) - Health Technology Assessment (UK)

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NL3090 NTR3244	
Study name	Perioperative Transfusion Study (PETS): does a liberal transfusion protocol improve outcome in high-risk cardiovascular patients undergoing non-cardiac surgery?
Methods	RCT
Participants	Elective high-risk cardiac surgery participants Estimated enrolment: 100
Interventions	Liberal group: 11 g/dL transfusion threshold Restrictive group: 9.7 g/dL transfusion threshold
Outcomes	Troponin elevation above 99th percentile
Starting date	August 2015
Contact information	Felix van Lier; f.vanlier@erasmusmc.nl
Notes	Trial registration (prospective): NTR3244 (https://www.trialregister.nl/trial/3090) Funding: not specified other than 'initiator' (presumed, investigator)

Abbreviations
CIHR: Canadian Institutes of Health Research
Hb: haemoglobin concentration
HSCT: haematopoietic stem cell transplantation
ICU: intensive care unit
IHD: ischaemic heart disease
MACE: major adverse cardiac events
MDS: myelodysplastic syndromes
NHSBT: National Health Service Blood and Transplant (UK)
PAD: peripheral arterial disease
RBCs: red blood cells
RCT: randomised controlled trial
STEMI: ST-segment elevation myocardial infarction

DATA AND ANALYSES

Comparison 1. Mortality at 30 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 30-Day mortality	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
1.2 30-Day mortality subgroup by restrictive haemoglobin level	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
1.2.1 Restrictive 7.0 g/dL to 7.5 g/dL	15	11572	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.19]
1.2.2 Restrictive < 8.0 g/dL to 9.0 g/dL	16	5157	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.75, 1.24]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 30-Day mortality subgroup analysis by clinical specialties	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
1.3.1 Cardiac surgery	4	7441	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]
1.3.2 Orthopaedic surgery	8	3111	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.75, 1.79]
1.3.3 Vascular	2	157	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.25]
1.3.4 Acute blood loss/trauma	3	1522	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.43, 0.97]
1.3.5 Critical care	9	3529	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.32]
1.3.6 Acute myocardial infarction	3	820	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.38, 6.88]
1.3.7 Haematological malignancies	2	149	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.07, 1.95]
1.4 30-Day mortality by clinical specialties: myocardial infarction vs all others	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
1.4.1 Myocardial infarction	3	820	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.38, 6.88]
1.4.2 All but myocardial infarction	28	15909	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
1.5 Mortality by cardiac surgery, vascular surgery, myocardial infarction, and all others	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.14]
1.5.1 Cardiac surgery	4	7441	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.33]
1.5.2 Myocardial infarction	3	820	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.38, 6.88]
1.5.3 Vascular surgery	2	157	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.25]
1.5.4 Others	22	8311	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.19]

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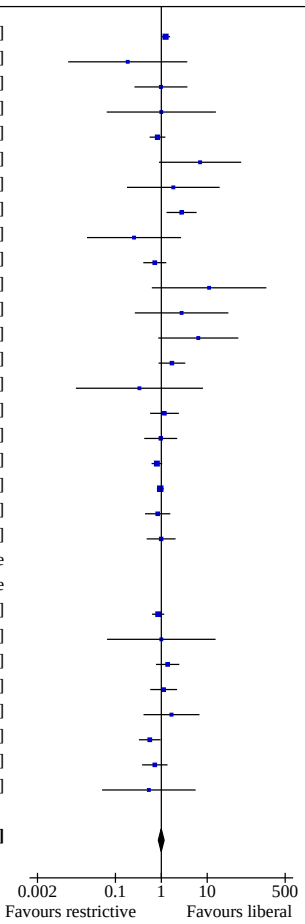
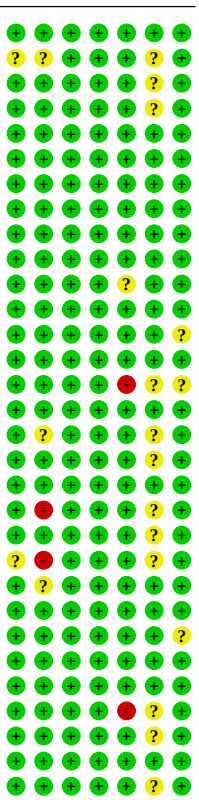
Analysis 1.1. Comparison 1: Mortality at 30 days, Outcome 1: 30-Day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99 , 1.55]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40 , 1.28]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26 , 28.95]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.5%	0.95 [0.80 , 1.13]
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44 , 1.57]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Laine 2018	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76 , 2.46]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32 , 0.97]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Total (95% CI)		**8321**		**8408**	**100.0%**	**0.99 [0.86 , 1.15]**
Total events:	670		689			

Risk Ratio M-H, Random, 95% CI



Risk of Bias



Heterogeneity: Tau² = 0.03; Chi² = 40.06, df = 28 (P = 0.07); I² = 30%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Objective outcomes
(D) Blinding of outcome assessment (detection bias): Objective measures
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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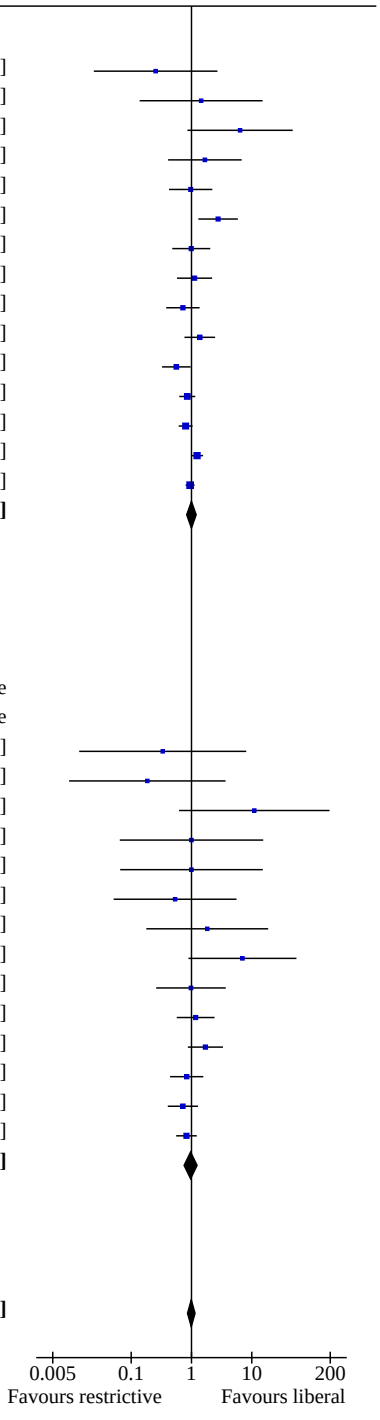
Analysis 1.2. Comparison 1: Mortality at 30 days, Outcome 2: 30-Day mortality subgroup by restrictive haemoglobin level

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Restrictive 7.0 g/dL to 7.5 g/dL						
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Gillies 2020	2	36	1	26	0.4%	1.44 [0.14 , 15.10]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Hébert 1995	8	33	9	36	2.5%	0.97 [0.42 , 2.22]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Murphy 2015	26	1000	19	1003	4.4%	1.37 [0.76 , 2.46]
Villanueva 2013	19	416	34	417	4.9%	0.56 [0.32 , 0.97]
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Hébert 1999	78	418	98	420	10.8%	0.80 [0.61 , 1.04]
Bergamin 2017	84	151	67	149	12.0%	1.24 [0.99 , 1.55]
Holst 2014	168	502	175	496	13.8%	0.95 [0.80 , 1.13]
Subtotal (95% CI)		**5805**		**5767**	**73.9%**	**1.00 [0.83 , 1.19]**
Total events:	537		549			
Heterogeneity: Tau² = 0.04; Chi² = 26.15, df = 14 (P = 0.02); I² = 46%						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.2.2 Restrictive < 8.0 g/dL to 9.0 g/dL						
Lotke 1999	0	62	0	65		Not estimable
Laine 2018	0	40	0	40		Not estimable
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Jairath 2015	14	257	25	382	3.9%	0.83 [0.44 , 1.57]
Ducrocq 2021	19	342	25	324	4.5%	0.72 [0.40 , 1.28]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Subtotal (95% CI)		**2526**		**2631**	**26.1%**	**0.97 [0.75 , 1.24]**
Total events:	133		140			
Heterogeneity: Tau² = 0.01; Chi² = 13.35, df = 13 (P = 0.42); I² = 3%						
Test for overall effect: Z = 0.27 (P = 0.78)						
Total (95% CI)		**8331**		**8398**	**100.0%**	**0.99 [0.86 , 1.14]**
Total events:	670		689			
Heterogeneity: Tau² = 0.03; Chi² = 39.41, df = 28 (P = 0.07); I² = 29%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.83), I² = 0%						



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Analysis 1.3. Comparison 1: Mortality at 30 days, Outcome 3: 30-Day mortality subgroup analysis by clinical specialties

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Cardiac surgery						
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Laine 2018	0	40	0	40		Not estimable
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Murphy 2015	26	1000	19	1003	4.4%	1.37 [0.76 , 2.46]
Subtotal (95% CI)		**3716**		**3725**	**17.3%**	**0.99 [0.74 , 1.33]**
Total events:	115		119			
Heterogeneity: Tau² = 0.01; Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.04 (P = 0.96)						
1.3.2 Orthopaedic surgery						
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	36	1	26	0.4%	1.44 [0.14 , 15.10]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Lotke 1999	0	62	0	65		Not estimable
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Subtotal (95% CI)		**1562**		**1549**	**13.1%**	**1.16 [0.75 , 1.79]**
Total events:	77		70			
Heterogeneity: Tau² = 0.05; Chi² = 7.02, df = 6 (P = 0.32); I² = 15%						
Test for overall effect: Z = 0.65 (P = 0.52)						
1.3.3 Vascular						
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Subtotal (95% CI)		**79**		**78**	**1.4%**	**0.98 [0.30 , 3.25]**
Total events:	5		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.3.4 Acute blood loss/trauma						
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Jairath 2015	14	257	25	382	3.9%	0.83 [0.44 , 1.57]
Villanueva 2013	19	416	34	417	4.9%	0.56 [0.32 , 0.97]
Subtotal (95% CI)		**699**		**823**	**9.0%**	**0.65 [0.43 , 0.97]**
Total events:	33		61			
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
1.3.5 Critical care						
Bergamin 2017	84	151	67	149	12.0%	1.24 [0.99 , 1.55]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Hébert 1995	8	33	9	36	2.5%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.8%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.8%	0.95 [0.80 , 1.13]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Subtotal (95% CI)		**1767**		**1762**	**53.2%**	**1.06 [0.85 , 1.32]**
Total events:	410		403			

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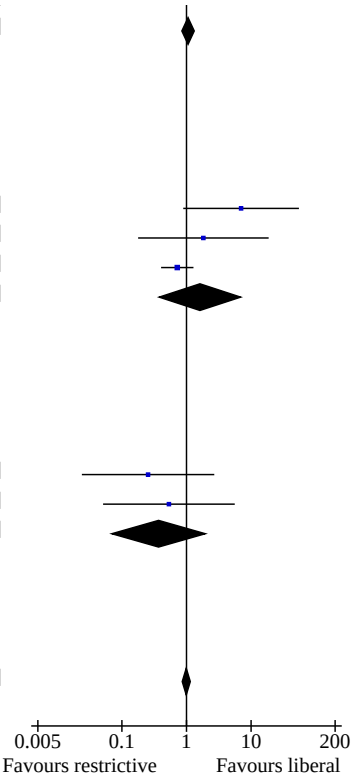
Analysis 1.3. (Continued)

Subtotal (95% CI)		**1767**		**1762**	**53.2%**	**1.06 [0.85 , 1.32]**
Total events:	410		403			
Heterogeneity: Tau² = 0.05; Chi² = 17.79, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 0.49 (P = 0.62)						
1.3.6 Acute myocardial infarction						
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
Ducrocq 2021	19	342	25	324	4.5%	0.72 [0.40 , 1.28]
Subtotal (95% CI)		**420**		**400**	**5.4%**	**1.61 [0.38 , 6.88]**
Total events:	28		27			
Heterogeneity: Tau² = 0.99; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 0.65 (P = 0.52)						
1.3.7 Haematological malignancies						
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**88**		**61**	**0.7%**	**0.37 [0.07 , 1.95]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**8331**		**8398**	**100.0%**	**0.99 [0.86 , 1.14]**
Total events:	670		689			
Heterogeneity: Tau² = 0.03; Chi² = 39.41, df = 28 (P = 0.07); I² = 29%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 6.73, df = 6 (P = 0.35), I² = 10.9%						



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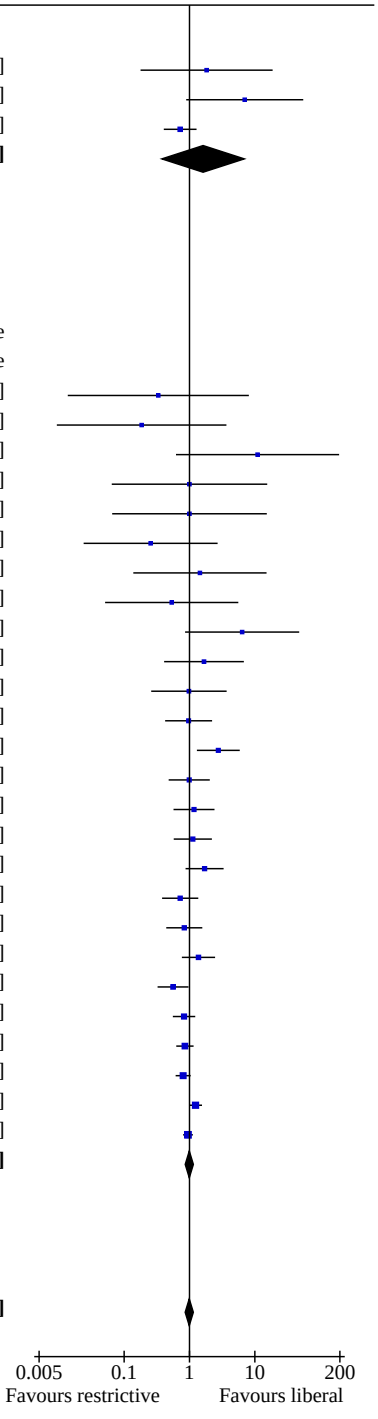
Analysis 1.4. Comparison 1: Mortality at 30 days, Outcome 4: 30-Day mortality by clinical specialties: myocardial infarction vs all others

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Myocardial infarction						
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Ducrocq 2021	19	342	25	324	4.5%	0.72 [0.40 , 1.28]
Subtotal (95% CI)		**420**		**400**	**5.4%**	**1.61 [0.38 , 6.88]**
Total events:	28		27			
Heterogeneity: Tau² = 0.99; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 0.65 (P = 0.52)						
1.4.2 All but myocardial infarction						
Lotke 1999	0	62	0	65		Not estimable
Laine 2018	0	40	0	40		Not estimable
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Gillies 2020	2	36	1	26	0.4%	1.44 [0.14 , 15.10]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Hébert 1995	8	33	9	36	2.5%	0.97 [0.42 , 2.22]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Jairath 2015	14	257	25	382	3.9%	0.83 [0.44 , 1.57]
Murphy 2015	26	1000	19	1003	4.4%	1.37 [0.76 , 2.46]
Villanueva 2013	19	416	34	417	4.9%	0.56 [0.32 , 0.97]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Hébert 1999	78	418	98	420	10.8%	0.80 [0.61 , 1.04]
Bergamin 2017	84	151	67	149	12.0%	1.24 [0.99 , 1.55]
Holst 2014	168	502	175	496	13.8%	0.95 [0.80 , 1.13]
Subtotal (95% CI)		**7911**		**7998**	**94.6%**	**0.99 [0.86 , 1.15]**
Total events:	642		662			
Heterogeneity: Tau² = 0.03; Chi² = 34.56, df = 25 (P = 0.10); I² = 28%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		**8331**		**8398**	**100.0%**	**0.99 [0.86 , 1.14]**
Total events:	670		689			
Heterogeneity: Tau² = 0.03; Chi² = 39.41, df = 28 (P = 0.07); I² = 29%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						



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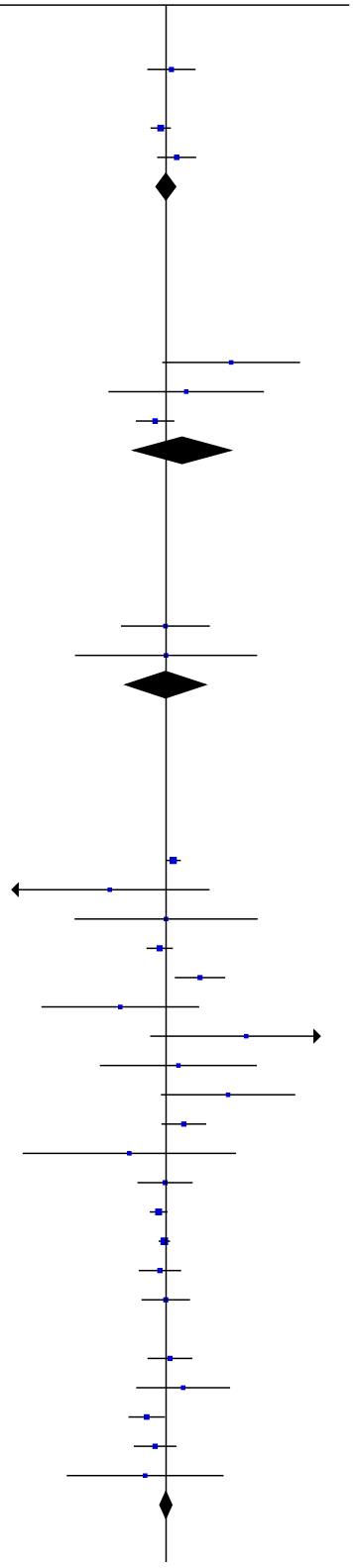
Analysis 1.5. Comparison 1: Mortality at 30 days, Outcome 5: Mortality by cardiac surgery, vascular surgery, myocardial infarction, and all others

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Cardiac surgery						
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Laine 2018	0	40	0	40		Not estimable
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Murphy 2015	26	1000	19	1003	4.4%	1.37 [0.76 , 2.46]
Subtotal (95% CI)		**3716**		**3725**	**17.3%**	**0.99 [0.74 , 1.33]**
Total events:	115		119			
Heterogeneity: Tau² = 0.01; Chi² = 2.32, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.04 (P = 0.96)						
1.5.2 Myocardial infarction						
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
Ducrocq 2021	19	342	25	324	4.5%	0.72 [0.40 , 1.28]
Subtotal (95% CI)		**420**		**400**	**5.4%**	**1.61 [0.38 , 6.88]**
Total events:	28		27			
Heterogeneity: Tau² = 0.99; Chi² = 4.89, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 0.65 (P = 0.52)						
1.5.3 Vascular surgery						
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Subtotal (95% CI)		**79**		**78**	**1.4%**	**0.98 [0.30 , 3.25]**
Total events:	5		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
1.5.4 Others						
Bergamin 2017	84	151	67	149	12.0%	1.24 [0.99 , 1.55]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	36	1	26	0.4%	1.44 [0.14 , 15.10]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hébert 1995	8	33	9	36	2.5%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.8%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.8%	0.95 [0.80 , 1.13]
Jairath 2015	14	257	25	382	3.9%	0.83 [0.44 , 1.57]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Lotke 1999	0	62	0	65		Not estimable
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	4.9%	0.56 [0.32 , 0.97]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**4116**		**4195**	**76.0%**	**0.99 [0.83 , 1.19]**
Total events:	522		538			
Heterogeneity: Tau² = 0.04; Chi² = 32.23, df = 20 (P = 0.04); I² = 38%						



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Analysis 1.5. (Continued)

Total events: 522 538

Heterogeneity: Tau² = 0.04; Chi² = 32.23, df = 20 (P = 0.04); I² = 38%

Test for overall effect: Z = 0.08 (P = 0.94)

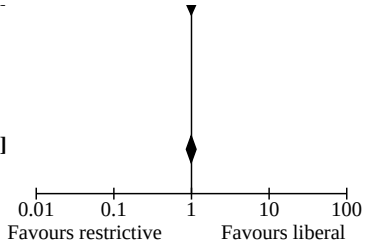
Total (95% CI) **8331** **8398** **100.0%** **0.99 [0.86 , 1.14]**

Total events: 670 689

Heterogeneity: Tau² = 0.03; Chi² = 39.41, df = 28 (P = 0.07); I² = 29%

Test for overall effect: Z = 0.12 (P = 0.91)

Test for subgroup differences: Chi² = 0.43, df = 3 (P = 0.93), I² = 0%



Comparison 2. Subgroup analysis by prospective registration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 30-Day mortality	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
2.1.1 Prospectively registered trials	18	12932	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.31]
2.1.2 Trials without prospective registration	13	3797	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 1.00]

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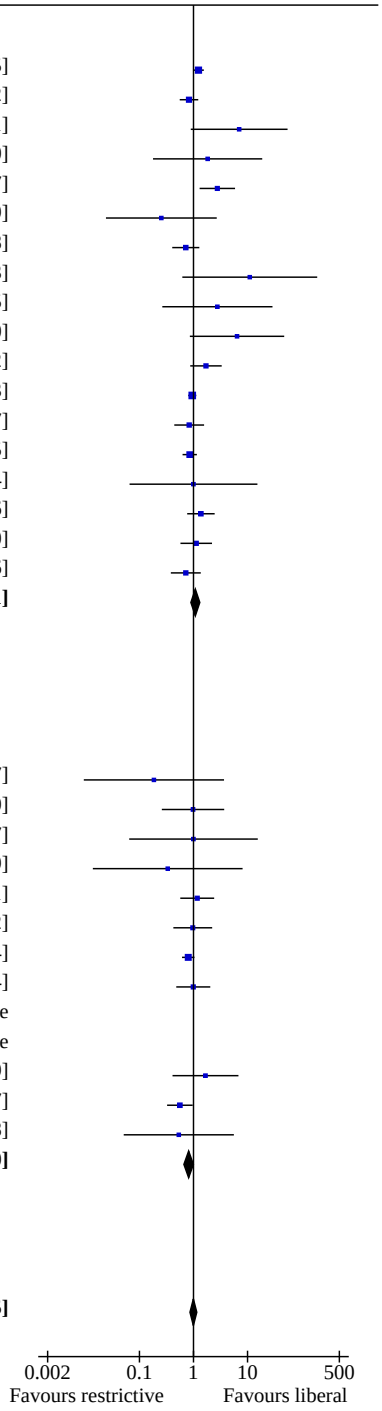
Analysis 2.1. Comparison 2: Subgroup analysis by prospective registration, Outcome 1: 30-Day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Prospectively registered trials						
Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99 , 1.55]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40 , 1.28]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26 , 28.95]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Holst 2014	168	502	175	496	13.5%	0.95 [0.80 , 1.13]
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44 , 1.57]
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76 , 2.46]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Subtotal (95% CI)		**6427**		**6505**	**72.1%**	**1.08 [0.89 , 1.31]**
Total events:	525		508			
Heterogeneity: Tau² = 0.05; Chi² = 30.29, df = 17 (P = 0.02); I² = 44%						
Test for overall effect: Z = 0.81 (P = 0.42)						
2.1.2 Trials without prospective registration						
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61 , 1.04]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Laine 2018	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32 , 0.97]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**1894**		**1903**	**27.9%**	**0.81 [0.66 , 1.00]**
Total events:	145		181			
Heterogeneity: Tau² = 0.00; Chi² = 5.73, df = 10 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
Total (95% CI)		**8321**		**8408**	**100.0%**	**0.99 [0.86 , 1.15]**
Total events:	670		689			
Heterogeneity: Tau² = 0.03; Chi² = 40.06, df = 28 (P = 0.07); I² = 30%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Chi² = 4.06, df = 1 (P = 0.04), I² = 75.4%						



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Comparison 3. Sensitivity analysis by allocation concealment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 30-Day mortality	31	16729	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.86, 1.15]
3.1.1 Low risk of bias	26	15764	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.18]
3.1.2 Unclear or high risk of bias	5	965	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.39]

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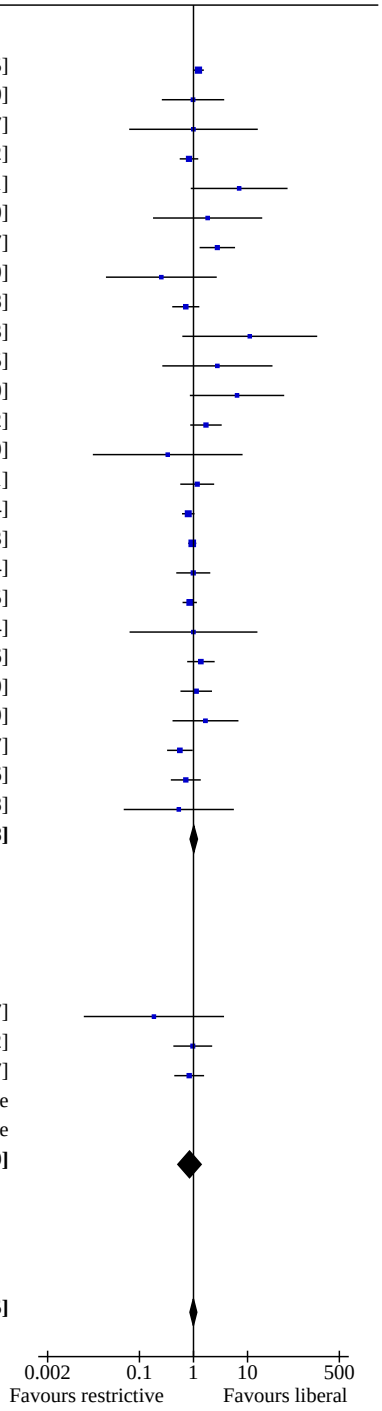
Analysis 3.1. Comparison 3: Sensitivity analysis by allocation concealment, Outcome 1: 30-Day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Low risk of bias						
Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99 , 1.55]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40 , 1.28]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26 , 28.95]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.5%	0.95 [0.80 , 1.13]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76 , 2.46]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32 , 0.97]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Subtotal (95% CI)		**7903**		**7861**	**93.2%**	**1.01 [0.87 , 1.18]**
Total events:	648		653			
Heterogeneity: Tau² = 0.04; Chi² = 38.61, df = 25 (P = 0.04); I² = 35%						
Test for overall effect: Z = 0.14 (P = 0.89)						
3.1.2 Unclear or high risk of bias						
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42 , 2.22]
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44 , 1.57]
Laine 2018	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Subtotal (95% CI)		**418**		**547**	**6.8%**	**0.84 [0.51 , 1.39]**
Total events:	22		36			
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**8321**		**8408**	**100.0%**	**0.99 [0.86 , 1.15]**
Total events:	670		689			
Heterogeneity: Tau² = 0.03; Chi² = 40.06, df = 28 (P = 0.07); I² = 30%						
Test for overall effect: Z = 0.07 (P = 0.94)						
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%						



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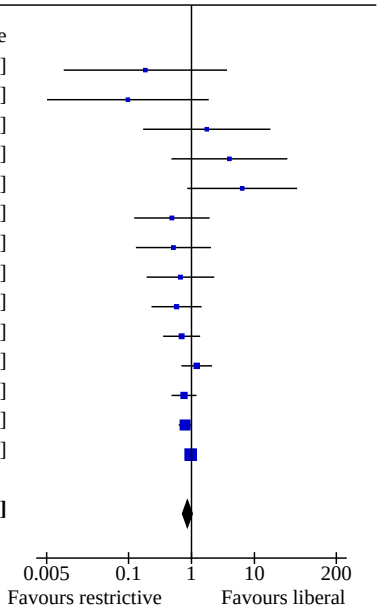
Comparison 4. Mortality: other time intervals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Hospital mortality	15	6597	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.03]
4.2 90-Day mortality	7	4143	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.02, 1.25]
4.3 6-Month mortality	2	4702	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.79, 1.22]

Analysis 4.1. Comparison 4: Mortality: other time intervals, Outcome 1: Hospital mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 1998	0	42	0	42		Not estimable
Blair 1986	0	26	2	24	0.4%	0.19 [0.01 , 3.67]
So-Osman 2013	0	299	3	204	0.4%	0.10 [0.01 , 1.88]
Cooper 2011	2	24	1	21	0.6%	1.75 [0.17 , 17.95]
Shehata 2012	4	25	1	25	0.7%	4.00 [0.48 , 33.33]
Gobatto 2019	7	23	1	21	0.8%	6.39 [0.86 , 47.70]
Koch 2017	3	363	6	354	1.6%	0.49 [0.12 , 1.93]
Bracey 1999	3	215	6	222	1.6%	0.52 [0.13 , 2.04]
Kola 2020	4	112	6	112	2.0%	0.67 [0.19 , 2.30]
Akyildiz 2018	6	71	13	89	3.5%	0.58 [0.23 , 1.45]
Carson 2011	14	1003	20	999	6.1%	0.70 [0.35 , 1.37]
Palmieri 2017	23	168	20	177	8.5%	1.21 [0.69 , 2.12]
Walsh 2013	19	51	24	49	11.9%	0.76 [0.48 , 1.20]
Hébert 1999	93	418	118	420	27.9%	0.79 [0.63 , 1.00]
Holst 2014	151	502	154	496	34.1%	0.97 [0.80 , 1.17]
Total (95% CI)		**3342**		**3255**	**100.0%**	**0.86 [0.72 , 1.03]**
Total events:	329		375			

Heterogeneity: Tau² = 0.02; Chi² = 15.36, df = 13 (P = 0.29); I² = 15%
Test for overall effect: Z = 1.67 (P = 0.10)
Test for subgroup differences: Not applicable



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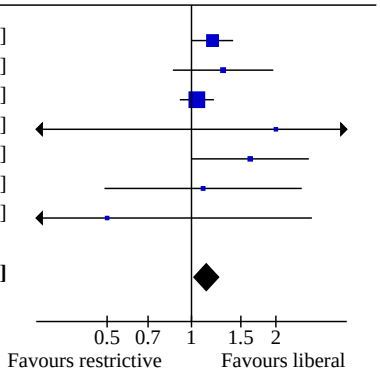
Analysis 4.2. Comparison 4: Mortality: other time intervals, Outcome 2: 90-Day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergamin 2017	106	151	88	149	35.5%	1.19 [1.00 , 1.41]
Gregersen 2015	40	144	30	140	6.0%	1.30 [0.86 , 1.96]
Holst 2014	223	496	216	502	52.0%	1.04 [0.91 , 1.20]
Møller 2019	2	29	1	29	0.2%	2.00 [0.19 , 20.86]
Murphy 2015	42	1000	26	1003	4.4%	1.62 [1.00 , 2.62]
Parker 2013	11	100	10	100	1.6%	1.10 [0.49 , 2.47]
Tay 2020	2	150	4	150	0.4%	0.50 [0.09 , 2.69]
Total (95% CI)		**2070**		**2073**	**100.0%**	**1.13 [1.02 , 1.25]**
Total events:	426		375			

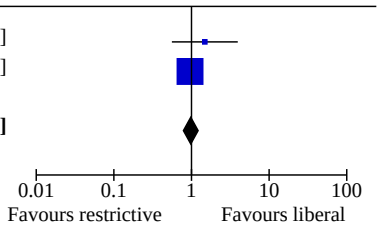
Heterogeneity: Tau² = 0.00; Chi² = 5.28, df = 6 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Mortality: other time intervals, Outcome 3: 6-Month mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2013	8	44	6	49	4.9%	1.48 [0.56 , 3.94]
Mazer 2017	141	2291	149	2318	95.1%	0.96 [0.77 , 1.20]
Total (95% CI)		**2335**		**2367**	**100.0%**	**0.98 [0.79 , 1.22]**
Total events:	149		155			

Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable



Comparison 5. Morbidity: clinical outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Cardiac events	11	5577	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.80, 1.32]
5.2 Myocardial infarction	23	14370	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.24]
5.3 Congestive heart failure	16	7247	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.53, 1.29]
5.4 Cerebrovascular accident (CVA) - stroke	19	13985	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.64, 1.09]
5.5 Rebleeding	8	3412	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.09]
5.6 Sepsis/bacteraemia	9	4352	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.86, 1.30]
5.7 Pneumonia	16	6666	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.13]
5.8 Infection	25	17104	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.07]

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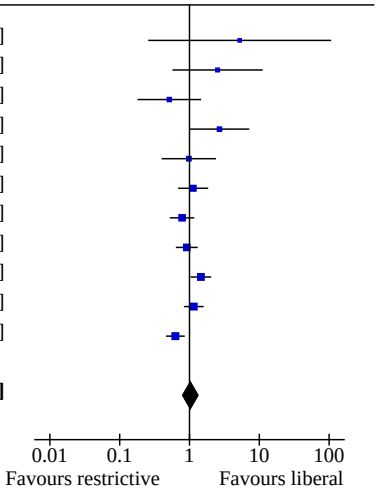
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.9 Thromboembolism	13	4201	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.65, 1.88]
5.10 Renal failure	15	12531	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.16]
5.11 Mental confusion	9	6442	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.88, 1.40]

Analysis 5.1. Comparison 5: Morbidity: clinical outcomes, Outcome 1: Cardiac events

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Lotke 1999	2	62	0	65	0.7%	5.24 [0.26 , 106.98]
Gillies 2020 (1)	7	36	2	26	2.5%	2.53 [0.57 , 11.20]
Johnson 1992	4	20	7	18	4.5%	0.51 [0.18 , 1.47]
de Almeida 2015	14	101	5	97	4.9%	2.69 [1.01 , 7.18]
Bush 1997	8	50	8	49	5.6%	0.98 [0.40 , 2.40]
So-Osman 2013	30	299	27	304	11.1%	1.13 [0.69 , 1.85]
Ducrocq 2021 (2)	38	342	46	324	13.0%	0.78 [0.52 , 1.17]
Bracey 1999	44	212	49	216	13.9%	0.91 [0.64 , 1.31]
Carson 2011	76	1009	52	1007	14.3%	1.46 [1.04 , 2.05]
Hajjar 2010	60	249	53	253	14.6%	1.15 [0.83 , 1.59]
Hébert 1999	55	418	88	420	15.0%	0.63 [0.46 , 0.85]
Total (95% CI)		**2798**		**2779**	**100.0%**	**1.03 [0.80 , 1.32]**
Total events:	338		337			

Heterogeneity: Tau² = 0.09; Chi² = 24.09, df = 10 (P = 0.007); I² = 58%
Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable



Footnotes
(1) Gilles rates are for MACE
(2) Steg rates are for MACE

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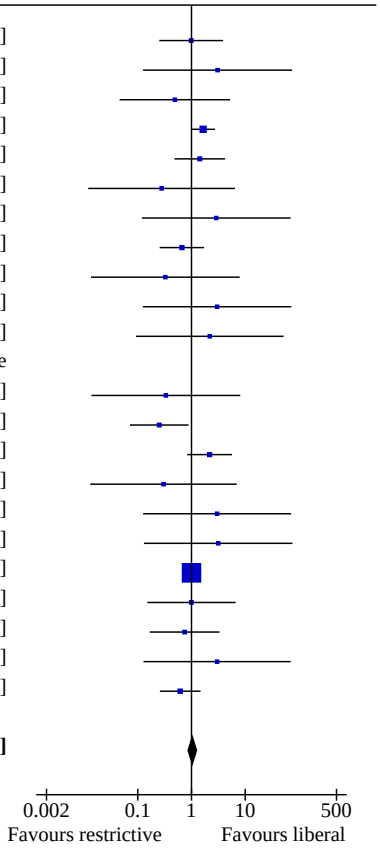
Analysis 5.2. Comparison 5: Morbidity: clinical outcomes, Outcome 2: Myocardial infarction

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergamin 2017	4	151	4	149	1.7%	0.99 [0.25 , 3.87]
Bracey 1999	1	212	0	216	0.3%	3.06 [0.13 , 74.61]
Bush 1997	1	50	2	49	0.6%	0.49 [0.05 , 5.23]
Carson 2011	38	1009	23	1007	12.3%	1.65 [0.99 , 2.75]
Carson 2013	7	54	5	55	2.7%	1.43 [0.48 , 4.22]
Cooper 2011	0	23	1	19	0.3%	0.28 [0.01 , 6.45]
de Almeida 2015	1	101	0	97	0.3%	2.88 [0.12 , 69.91]
Ducrocq 2021	7	342	10	324	3.5%	0.66 [0.26 , 1.72]
Fan 2014	0	94	1	92	0.3%	0.33 [0.01 , 7.91]
Foss 2009	1	60	0	60	0.3%	3.00 [0.12 , 72.20]
Gillies 2020	1	36	0	26	0.3%	2.19 [0.09 , 51.70]
Gobatto 2019	0	23	0	21		Not estimable
Grover 2006	0	109	1	109	0.3%	0.33 [0.01 , 8.09]
Hébert 1999	3	418	12	420	2.0%	0.25 [0.07 , 0.88]
Holst 2014	13	488	6	489	3.5%	2.17 [0.83 , 5.67]
Johnson 1992	0	20	1	18	0.3%	0.30 [0.01 , 6.97]
Laine 2018	1	40	0	40	0.3%	3.00 [0.13 , 71.51]
Lotke 1999	1	62	0	65	0.3%	3.14 [0.13 , 75.72]
Mazer 2017	144	2428	144	2429	63.7%	1.00 [0.80 , 1.25]
Møller 2019	2	29	2	29	0.9%	1.00 [0.15 , 6.63]
Murphy 2015	3	987	4	981	1.4%	0.75 [0.17 , 3.32]
Shehata 2012	1	25	0	25	0.3%	3.00 [0.13 , 70.30]
Villanueva 2013	8	444	13	445	4.2%	0.62 [0.26 , 1.47]
Total (95% CI)		**7205**		**7165**	**100.0%**	**1.04 [0.87 , 1.24]**
Total events:	237		229			

Heterogeneity: Tau² = 0.00; Chi² = 18.63, df = 21 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable



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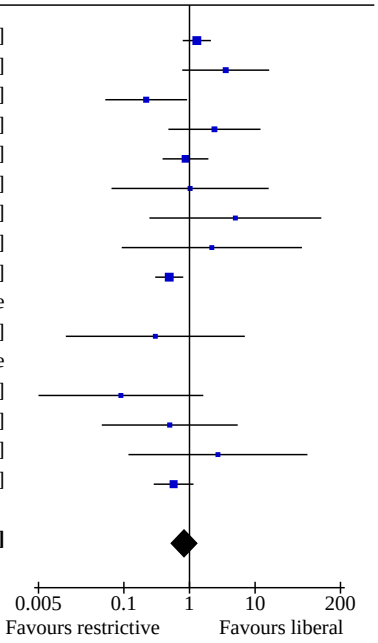
Analysis 5.3. Comparison 5: Morbidity: clinical outcomes, Outcome 3: Congestive heart failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2011	35	1009	27	1007	18.6%	1.29 [0.79 , 2.12]
Carson 2013	7	54	2	55	6.3%	3.56 [0.78 , 16.40]
Cooper 2011	2	24	8	21	6.9%	0.22 [0.05 , 0.92]
de Almeida 2015	5	101	2	97	5.8%	2.40 [0.48 , 12.08]
Ducrocq 2021	11	342	12	324	13.5%	0.87 [0.39 , 1.94]
Fan 2014	1	94	1	96	2.4%	1.02 [0.06 , 16.09]
Foss 2009	2	60	0	60	2.0%	5.00 [0.25 , 102.00]
Gillies 2020	1	36	0	26	1.8%	2.19 [0.09 , 51.70]
Hébert 1999	22	418	45	420	18.7%	0.49 [0.30 , 0.80]
Holst 2014	0	488	0	489		Not estimable
Johnson 1992	0	20	1	18	1.9%	0.30 [0.01 , 6.97]
Kola 2020	0	112	0	112		Not estimable
Lacroix 2007	0	320	5	317	2.2%	0.09 [0.01 , 1.62]
Parker 2013	1	100	2	100	3.0%	0.50 [0.05 , 5.43]
Stanworth 2020	1	20	0	18	1.9%	2.71 [0.12 , 62.70]
Villanueva 2013	12	444	21	445	15.2%	0.57 [0.29 , 1.15]
Total (95% CI)		**3642**		**3605**	**100.0%**	**0.83 [0.53 , 1.29]**
Total events:	100		126			

Heterogeneity: Tau² = 0.21; Chi² = 22.06, df = 13 (P = 0.05); I² = 41%
Test for overall effect: Z = 0.85 (P = 0.40)
Test for subgroup differences: Not applicable



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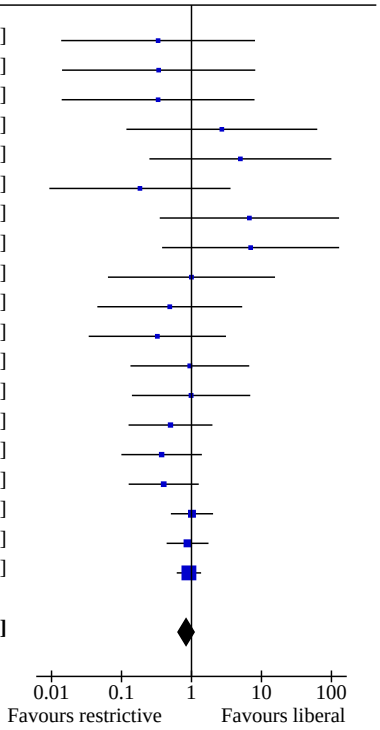
Analysis 5.4. Comparison 5: Morbidity: clinical outcomes, Outcome 4: Cerebrovascular accident (CVA) - stroke

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Parker 2013	0	100	1	100	0.7%	0.33 [0.01 , 8.09]
Carson 2013	0	54	1	55	0.7%	0.34 [0.01 , 8.15]
Carson 1998	0	42	1	42	0.7%	0.33 [0.01 , 7.96]
Johnson 1992	1	20	0	18	0.7%	2.71 [0.12 , 62.70]
Møller 2019	2	29	0	29	0.8%	5.00 [0.25 , 99.82]
Gobatto 2019	0	23	2	21	0.8%	0.18 [0.01 , 3.61]
de Almeida 2015	3	101	0	97	0.8%	6.73 [0.35 , 128.52]
Shehata 2012	3	25	0	25	0.8%	7.00 [0.38 , 128.87]
Foss 2009	1	60	1	60	0.9%	1.00 [0.06 , 15.62]
Fan 2014	1	94	2	92	1.2%	0.49 [0.05 , 5.30]
Koch 2017	1	363	3	354	1.4%	0.33 [0.03 , 3.11]
Ducrocq 2021	2	342	2	324	1.9%	0.95 [0.13 , 6.69]
Bergamin 2017	2	151	2	149	1.9%	0.99 [0.14 , 6.91]
Villanueva 2013	3	444	6	445	3.7%	0.50 [0.13 , 1.99]
Carson 2011	3	1009	8	1007	4.0%	0.37 [0.10 , 1.41]
Holst 2014	4	488	10	489	5.3%	0.40 [0.13 , 1.27]
Hajjar 2010	15	249	15	253	14.7%	1.02 [0.51 , 2.03]
Murphy 2015	15	989	17	985	14.9%	0.88 [0.44 , 1.75]
Mazer 2017	45	2428	49	2429	44.0%	0.92 [0.62 , 1.37]
Total (95% CI)		**7011**		**6974**	**100.0%**	**0.84 [0.64 , 1.09]**
Total events:	101		120			

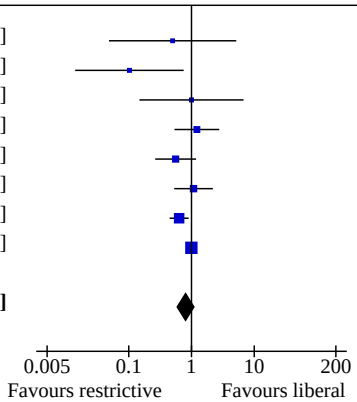
Heterogeneity: Tau² = 0.00; Chi² = 12.80, df = 18 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Morbidity: clinical outcomes, Outcome 5: Rebleeding

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Shehata 2012	1	25	2	25	1.6%	0.50 [0.05 , 5.17]
Blair 1986	1	26	9	24	2.2%	0.10 [0.01 , 0.75]
Laine 2018	2	40	2	40	2.4%	1.00 [0.15 , 6.76]
Hajjar 2010	12	249	10	253	10.2%	1.22 [0.54 , 2.77]
Jairath 2015	9	257	24	383	11.6%	0.56 [0.26 , 1.18]
Kola 2020	14	112	13	112	12.6%	1.08 [0.53 , 2.19]
Villanueva 2013	45	444	71	445	25.7%	0.64 [0.45 , 0.90]
Holst 2014	147	488	148	489	33.6%	1.00 [0.82 , 1.20]
Total (95% CI)		**1641**		**1771**	**100.0%**	**0.80 [0.59 , 1.09]**
Total events:	231		279			

Heterogeneity: Tau² = 0.06; Chi² = 12.24, df = 7 (P = 0.09); I² = 43%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



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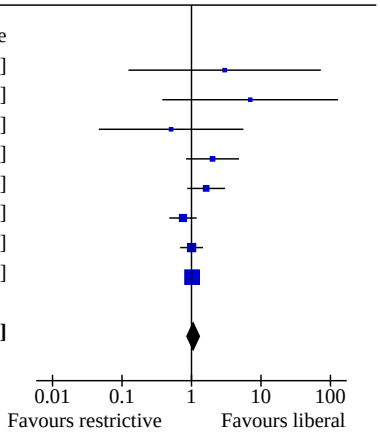
Analysis 5.6. Comparison 5: Morbidity: clinical outcomes, Outcome 6: Sepsis/bacteraemia

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2013	0	54	0	55		Not estimable
Parker 2013	1	100	0	100	0.4%	3.00 [0.12 , 72.77]
Shehata 2012	3	25	0	25	0.5%	7.00 [0.38 , 128.87]
So-Osman 2013	1	299	2	304	0.7%	0.51 [0.05 , 5.58]
Gobatto 2019	11	23	5	21	5.1%	2.01 [0.84 , 4.82]
de Almeida 2015	22	101	13	97	9.3%	1.63 [0.87 , 3.04]
Hébert 1999	30	418	40	420	15.9%	0.75 [0.48 , 1.19]
Palmieri 2017	40	168	42	177	20.7%	1.00 [0.69 , 1.46]
Murphy 2015	214	983	210	982	47.3%	1.02 [0.86 , 1.20]
Total (95% CI)		**2171**		**2181**	**100.0%**	**1.06 [0.86 , 1.30]**
Total events:	322		312			

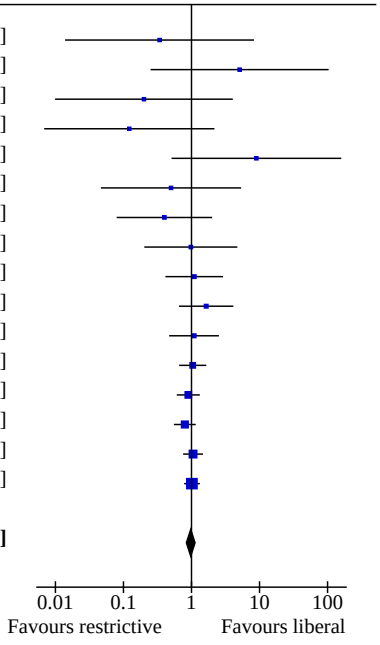
Heterogeneity: Tau² = 0.02; Chi² = 8.56, df = 7 (P = 0.29); I² = 18%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Morbidity: clinical outcomes, Outcome 7: Pneumonia

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
So-Osman 2013	0	299	1	304	0.2%	0.34 [0.01 , 8.29]
Carson 2013	2	54	0	55	0.2%	5.09 [0.25 , 103.64]
Carson 1998	0	42	2	42	0.2%	0.20 [0.01 , 4.04]
Nielsen 2014	0	30	4	33	0.3%	0.12 [0.01 , 2.17]
Shehata 2012	4	25	0	25	0.3%	9.00 [0.51 , 158.85]
Foss 2009	1	60	2	60	0.4%	0.50 [0.05 , 5.37]
Parker 2013	2	100	5	100	0.8%	0.40 [0.08 , 2.01]
Fan 2014	3	94	3	92	0.9%	0.98 [0.20 , 4.72]
de Almeida 2015	8	101	7	97	2.2%	1.10 [0.41 , 2.91]
Gobatto 2019	9	23	5	21	2.5%	1.64 [0.66 , 4.12]
Lacroix 2007	11	320	10	317	3.0%	1.09 [0.47 , 2.53]
Gregersen 2015	30	144	28	140	10.1%	1.04 [0.66 , 1.65]
Villanueva 2013	43	444	48	445	14.0%	0.90 [0.61 , 1.33]
Carson 2011	48	1009	60	1007	15.6%	0.80 [0.55 , 1.16]
Palmieri 2017	49	168	49	177	19.0%	1.05 [0.75 , 1.47]
Hébert 1999	87	418	86	420	30.2%	1.02 [0.78 , 1.33]
Total (95% CI)		**3331**		**3335**	**100.0%**	**0.97 [0.84 , 1.13]**
Total events:	297		310			

Heterogeneity: Tau² = 0.00; Chi² = 11.48, df = 15 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)
Test for subgroup differences: Not applicable



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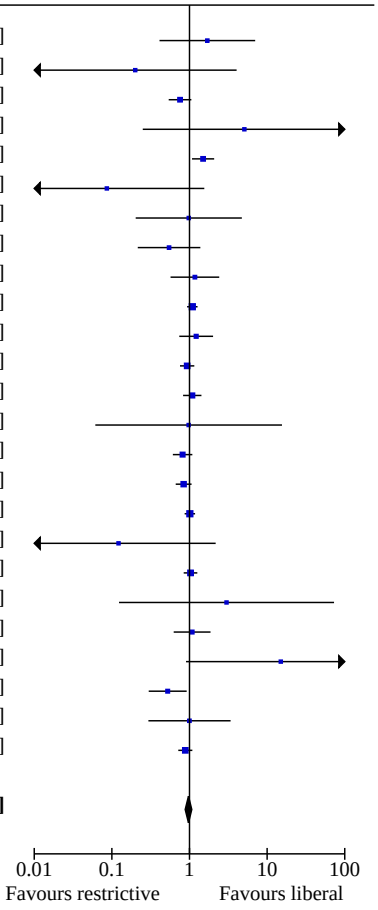
Analysis 5.8. Comparison 5: Morbidity: clinical outcomes, Outcome 8: Infection

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bracey 1999	5	212	3	216	0.5%	1.70 [0.41 , 7.02]
Carson 1998	0	42	2	42	0.1%	0.20 [0.01 , 4.04]
Carson 2011	56	1009	74	1007	5.6%	0.76 [0.54 , 1.06]
Carson 2013	2	54	0	55	0.1%	5.09 [0.25 , 103.64]
de Almeida 2015	53	101	34	97	5.8%	1.50 [1.08 , 2.08]
Ducrocq 2021	0	342	5	324	0.1%	0.09 [0.00 , 1.55]
Fan 2014	3	94	3	92	0.4%	0.98 [0.20 , 4.72]
Foss 2009	6	60	11	60	1.0%	0.55 [0.22 , 1.38]
Gillies 2020	13	36	8	26	1.6%	1.17 [0.57 , 2.42]
Gregersen 2015	104	144	93	140	11.9%	1.09 [0.93 , 1.27]
Hajjar 2010	30	249	25	253	3.1%	1.22 [0.74 , 2.01]
Hébert 1999	117	418	126	420	9.4%	0.93 [0.75 , 1.15]
Jairath 2015	67	257	92	383	7.3%	1.09 [0.83 , 1.42]
Koch 2017	1	363	1	354	0.1%	0.98 [0.06 , 15.53]
Lacroix 2007	65	320	79	317	6.8%	0.82 [0.61 , 1.09]
Mazer 2017	121	2428	144	2429	8.6%	0.84 [0.66 , 1.06]
Murphy 2015	238	936	240	954	11.9%	1.01 [0.87 , 1.18]
Nielsen 2014	0	30	4	33	0.1%	0.12 [0.01 , 2.17]
Palmieri 2017	89	168	91	177	9.8%	1.03 [0.84 , 1.26]
Parker 2013	1	100	0	100	0.1%	3.00 [0.12 , 72.77]
Prick 2014	24	211	22	209	2.7%	1.08 [0.63 , 1.87]
Shehata 2012	7	25	0	25	0.1%	15.00 [0.90 , 249.30]
So-Osman 2013	17	299	33	304	2.5%	0.52 [0.30 , 0.92]
Tay 2020	5	150	5	150	0.6%	1.00 [0.30 , 3.38]
Villanueva 2013	119	444	135	445	9.6%	0.88 [0.72 , 1.09]
Total (95% CI)		**8492**		**8612**	**100.0%**	**0.97 [0.88 , 1.07]**
Total events:	1143		1230			

Heterogeneity: Tau² = 0.01; Chi² = 35.34, df = 24 (P = 0.06); I² = 32%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



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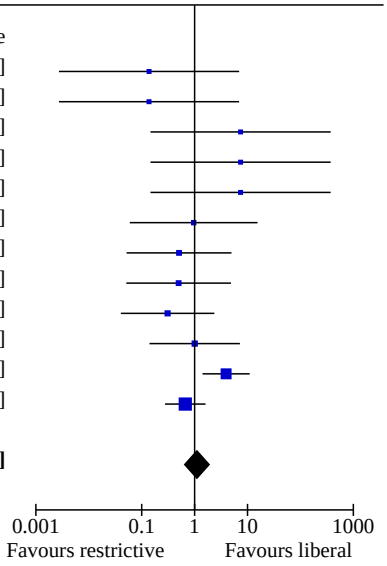
Analysis 5.9. Comparison 5: Morbidity: clinical outcomes, Outcome 9: Thromboembolism

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Laine 2018	0	40	0	40		Not estimable
Carson 2013	0	54	1	55	1.8%	0.14 [0.00 , 6.95]
So-Osman 2013	0	299	1	304	1.8%	0.14 [0.00 , 6.93]
Shehata 2012	1	25	0	25	1.8%	7.39 [0.15 , 372.38]
Carson 1998	1	42	0	42	1.8%	7.39 [0.15 , 372.38]
Parker 2013	1	100	0	100	1.8%	7.39 [0.15 , 372.38]
de Almeida 2015	1	101	1	97	3.6%	0.96 [0.06 , 15.47]
Foss 2009	1	60	2	60	5.4%	0.51 [0.05 , 4.97]
Fan 2014	1	94	2	92	5.4%	0.50 [0.05 , 4.85]
Gobatto 2019	1	23	3	21	6.8%	0.31 [0.04 , 2.36]
Prick 2014	2	226	2	227	7.2%	1.00 [0.14 , 7.18]
Møller 2019	18	29	8	29	26.5%	3.94 [1.41 , 10.98]
Carson 2011	8	1009	12	1007	36.0%	0.67 [0.28 , 1.61]
Total (95% CI)		**2102**		**2099**	**100.0%**	**1.11 [0.65 , 1.88]**
Total events:	35		32			

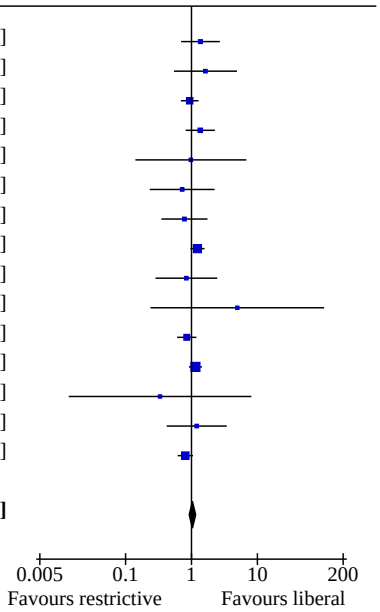
Heterogeneity: Chi² = 14.48, df = 11 (P = 0.21); I² = 24%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 5.10. Comparison 5: Morbidity: clinical outcomes, Outcome 10: Renal failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergamin 2017	18	151	13	149	2.7%	1.37 [0.69 , 2.69]
Bracey 1999	8	212	5	216	1.0%	1.63 [0.54 , 4.90]
de Almeida 2015	44	101	45	97	13.0%	0.94 [0.69 , 1.28]
Ducrocq 2021	33	342	23	324	4.8%	1.36 [0.82 , 2.26]
Fan 2014	2	94	2	92	0.3%	0.98 [0.14 , 6.80]
Gillies 2020	5	36	5	26	1.0%	0.72 [0.23 , 2.24]
Hajjar 2010	10	249	13	253	1.9%	0.78 [0.35 , 1.75]
Holst 2014	109	432	88	429	20.3%	1.23 [0.96 , 1.57]
Koch 2017	6	363	7	354	1.1%	0.84 [0.28 , 2.46]
Lacroix 2007	2	320	0	317	0.1%	4.95 [0.24 , 102.77]
Mazer 2017	61	2428	72	2429	11.0%	0.85 [0.61 , 1.19]
Murphy 2015	140	989	122	989	24.2%	1.15 [0.92 , 1.44]
Parker 2013	0	100	1	100	0.1%	0.33 [0.01 , 8.09]
Shehata 2012	6	25	5	25	1.1%	1.20 [0.42 , 3.43]
Villanueva 2013	78	444	97	445	17.3%	0.81 [0.62 , 1.05]
Total (95% CI)		**6286**		**6245**	**100.0%**	**1.03 [0.92 , 1.16]**
Total events:	522		498			

Heterogeneity: Tau² = 0.00; Chi² = 12.77, df = 14 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



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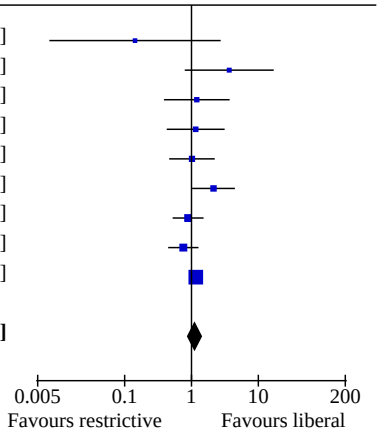
Analysis 5.11. Comparison 5: Morbidity: clinical outcomes, Outcome 11: Mental confusion

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Parker 2013	0	100	3	100	0.6%	0.14 [0.01 , 2.73]
Lotke 1999	7	62	2	65	2.2%	3.67 [0.79 , 16.99]
Foss 2009	6	60	5	60	4.0%	1.20 [0.39 , 3.72]
Gillies 2020	8	36	5	26	5.0%	1.16 [0.43 , 3.13]
So-Osman 2013	12	299	12	304	7.6%	1.02 [0.46 , 2.23]
Gregersen 2015	19	89	9	90	8.5%	2.13 [1.02 , 4.46]
Fan 2014	20	94	22	92	14.2%	0.89 [0.52 , 1.52]
Carson 2011	16	53	22	55	14.6%	0.75 [0.45 , 1.27]
Mazer 2017	306	2428	264	2429	43.2%	1.16 [0.99 , 1.35]
Total (95% CI)		**3221**		**3221**	**100.0%**	**1.11 [0.88 , 1.40]**
Total events:	394		344			

Heterogeneity: Tau² = 0.03; Chi² = 10.29, df = 8 (P = 0.24); I² = 22%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable



Comparison 6. Blood transfusions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Participants exposed to blood transfusion (all trials)	42	20057	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.53, 0.66]
6.2 Participants exposed to blood transfusion by clinical specialties	41	19977	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.53, 0.66]
6.2.1 Cardiac surgery	7	8598	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.66, 0.73]
6.2.2 Orthopaedic surgery	11	3969	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.38, 0.65]
6.2.3 Vascular surgery	2	157	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.08]
6.2.4 Acute blood loss/trauma	5	2416	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.23, 0.67]
6.2.5 Critical care	9	3529	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.77]
6.2.6 Acute myocardial infarction	3	821	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.28, 0.53]
6.2.7 Haematological malignancies	4	487	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.26]
6.3 Participants exposed to blood transfusion (by transfusion threshold)	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3.1 Difference between liberal and restrictive haemoglobin thresholds ≥ 2.0 g/dL	27	15072	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.50, 0.64]
6.3.2 Difference between liberal and restrictive haemoglobin thresholds < 2.0 g/dL	6	2966	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.02]
6.4 Participants exposed to blood transfusion by transfusion threshold	36	17954	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.51, 0.64]
6.4.1 Restrictive 7.0 g/dL to 7.5 g/dL	17	11919	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.48, 0.64]
6.4.2 Restrictive < 8.0 g/dL to 9.0 g/dL	19	6035	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.48, 0.72]
6.5 Units of blood transfused	17	6253	Mean Difference (IV, Random, 95% CI)	-1.21 [-1.67, -0.75]

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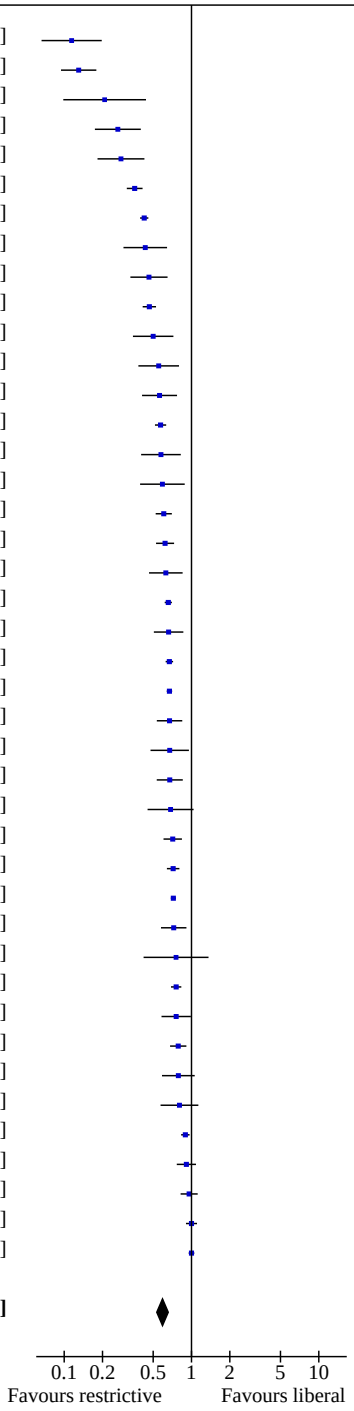
Analysis 6.1. Comparison 6: Blood transfusions, Outcome 1: Participants exposed to blood transfusion (all trials)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Parker 2013	11	100	100	100	1.6%	0.11 [0.07 , 0.20]
Prick 2014	33	261	251	258	2.2%	0.13 [0.09 , 0.18]
Blair 1986	5	26	24	24	1.1%	0.21 [0.10 , 0.44]
Lotke 1999	16	62	65	65	1.9%	0.26 [0.17 , 0.40]
Carson 2013	15	55	55	55	1.9%	0.28 [0.18 , 0.43]
Ducrocq 2021	122	342	323	324	2.7%	0.36 [0.31 , 0.41]
Carson 2011	415	1009	974	1007	2.8%	0.43 [0.39 , 0.46]
Gillies 2020	15	36	25	26	2.0%	0.43 [0.29 , 0.64]
Carson 1998	19	42	41	42	2.2%	0.46 [0.33 , 0.65]
Lacroix 2007	146	320	310	317	2.7%	0.47 [0.41 , 0.53]
Foss 2009	22	60	44	60	2.1%	0.50 [0.35 , 0.72]
Cooper 2011	13	24	21	21	2.1%	0.55 [0.38 , 0.80]
Hébert 1995	18	33	35	36	2.2%	0.56 [0.41 , 0.77]
Villanueva 2013	219	444	384	445	2.8%	0.57 [0.52 , 0.63]
Gobatto 2019	13	23	21	21	2.1%	0.58 [0.40 , 0.82]
Shehata 2012	13	25	22	25	2.0%	0.59 [0.39 , 0.88]
Hajjar 2010	118	249	198	253	2.7%	0.61 [0.52 , 0.70]
Tay 2020	80	150	129	150	2.6%	0.62 [0.53 , 0.73]
Laine 2018	22	40	35	40	2.3%	0.63 [0.46 , 0.85]
Holst 2014	326	502	490	496	2.8%	0.66 [0.62 , 0.70]
Møller 2019	19	29	29	29	2.4%	0.66 [0.51 , 0.86]
Hébert 1999	280	418	420	420	2.8%	0.67 [0.63 , 0.72]
Murphy 2015	637	1000	952	1003	2.8%	0.67 [0.64 , 0.70]
Bergamin 2017	62	151	91	149	2.5%	0.67 [0.53 , 0.85]
de Almeida 2015	33	101	47	97	2.1%	0.67 [0.48 , 0.95]
So-Osman 2013	79	299	119	304	2.5%	0.67 [0.53 , 0.85]
Topley 1956	8	12	10	10	1.9%	0.68 [0.45 , 1.04]
Jairath 2015	133	403	247	533	2.6%	0.71 [0.60 , 0.84]
Koch 2017	195	363	265	354	2.7%	0.72 [0.64 , 0.80]
Mazer 2017	1271	2430	1765	2430	2.8%	0.72 [0.69 , 0.75]
Bracey 1999	74	212	104	216	2.5%	0.72 [0.58 , 0.91]
Nielsen 2014	11	30	16	33	1.5%	0.76 [0.42 , 1.36]
Gregersen 2015	109	144	140	140	2.8%	0.76 [0.69 , 0.83]
Johnson 1992	15	20	18	18	2.4%	0.76 [0.58 , 0.99]
Walsh 2013	40	51	49	49	2.7%	0.79 [0.68 , 0.91]
Fan 2014	41	96	52	96	2.3%	0.79 [0.59 , 1.06]
Grover 2006	37	109	46	109	2.2%	0.80 [0.57 , 1.13]
Palmieri 2017	141	168	166	177	2.8%	0.89 [0.83 , 0.97]
Bush 1997	40	50	43	49	2.6%	0.91 [0.77 , 1.08]
Webert 2008 (1)	26	29	29	31	2.7%	0.96 [0.82 , 1.12]
Stanworth 2020	20	20	18	18	2.8%	1.00 [0.91 , 1.10]
DeZern 2016	59	59	30	30	2.8%	1.00 [0.95 , 1.05]
Total (95% CI)		**9997**		**10060**	**100.0%**	**0.59 [0.53 , 0.66]**
Total events:	4971		8203			

Heterogeneity: Tau² = 0.10; Chi² = 1104.24, df = 41 (P < 0.00001); I² = 96%
Test for overall effect: Z = 9.93 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Three trials did not report the number of participants transfused; Kola -224 participants, Jansent 19 participants, Yakymendo - 133

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Analysis 6.2. Comparison 6: Blood transfusions, Outcome 2: Participants exposed to blood transfusion by clinical specialties

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Cardiac surgery						
Bracey 1999	74	212	104	216	2.5%	0.72 [0.58 , 0.91]
Hajjar 2010	118	249	198	253	2.7%	0.61 [0.52 , 0.70]
Johnson 1992	15	20	18	18	2.4%	0.76 [0.58 , 0.99]
Koch 2017	195	363	265	354	2.8%	0.72 [0.64 , 0.80]
Mazer 2017	1271	2430	1765	2430	2.9%	0.72 [0.69 , 0.75]
Murphy 2015	637	1000	952	1003	2.9%	0.67 [0.64 , 0.70]
Shehata 2012	13	25	22	25	2.0%	0.59 [0.39 , 0.88]
Subtotal (95% CI)		**4299**		**4299**	**18.3%**	**0.69 [0.66 , 0.73]**
Total events:	2323		3324			
Heterogeneity: Tau² = 0.00; Chi² = 9.34, df = 6 (P = 0.16); I² = 36%						
Test for overall effect: Z = 14.67 (P < 0.00001)						
6.2.2 Orthopaedic surgery						
Carson 1998	19	42	41	42	2.2%	0.46 [0.33 , 0.65]
Carson 2011	415	1009	974	1007	2.9%	0.43 [0.39 , 0.46]
Fan 2014	41	96	52	96	2.4%	0.79 [0.59 , 1.06]
Foss 2009	22	60	44	60	2.1%	0.50 [0.35 , 0.72]
Gillies 2020	15	36	25	26	2.1%	0.43 [0.29 , 0.64]
Gregersen 2015	109	144	140	140	2.8%	0.76 [0.69 , 0.83]
Grover 2006	37	109	46	109	2.2%	0.80 [0.57 , 1.13]
Lotke 1999	16	62	65	65	2.0%	0.26 [0.17 , 0.40]
Nielsen 2014	11	30	16	33	1.5%	0.76 [0.42 , 1.36]
Parker 2013	11	100	100	100	1.6%	0.11 [0.07 , 0.20]
So-Osman 2013	79	299	119	304	2.5%	0.67 [0.53 , 0.85]
Subtotal (95% CI)		**1987**		**1982**	**24.3%**	**0.49 [0.38 , 0.65]**
Total events:	775		1622			
Heterogeneity: Tau² = 0.17; Chi² = 170.27, df = 10 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 5.16 (P < 0.00001)						
6.2.3 Vascular surgery						
Bush 1997	40	50	43	49	2.7%	0.91 [0.77 , 1.08]
Møller 2019	19	29	29	29	2.4%	0.66 [0.51 , 0.86]
Subtotal (95% CI)		**79**		**78**	**5.1%**	**0.79 [0.57 , 1.08]**
Total events:	59		72			
Heterogeneity: Tau² = 0.04; Chi² = 4.01, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 1.47 (P = 0.14)						
6.2.4 Acute blood loss/trauma						
Blair 1986	5	26	24	24	1.2%	0.21 [0.10 , 0.44]
Jairath 2015	133	403	247	533	2.7%	0.71 [0.60 , 0.84]
Prick 2014	33	261	251	258	2.3%	0.13 [0.09 , 0.18]
Topley 1956	8	12	10	10	2.0%	0.68 [0.45 , 1.04]
Villanueva 2013	219	444	384	445	2.8%	0.57 [0.52 , 0.63]
Subtotal (95% CI)		**1146**		**1270**	**11.0%**	**0.39 [0.23 , 0.67]**
Total events:	398		916			
Heterogeneity: Tau² = 0.35; Chi² = 108.02, df = 4 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
6.2.5 Critical care						
Bergamin 2017	62	151	91	149	2.5%	0.67 [0.53 , 0.85]
de Almeida 2015	33	101	47	97	2.2%	0.67 [0.48 , 0.95]
Gobatto 2019	13	23	21	21	2.2%	0.58 [0.40 , 0.82]

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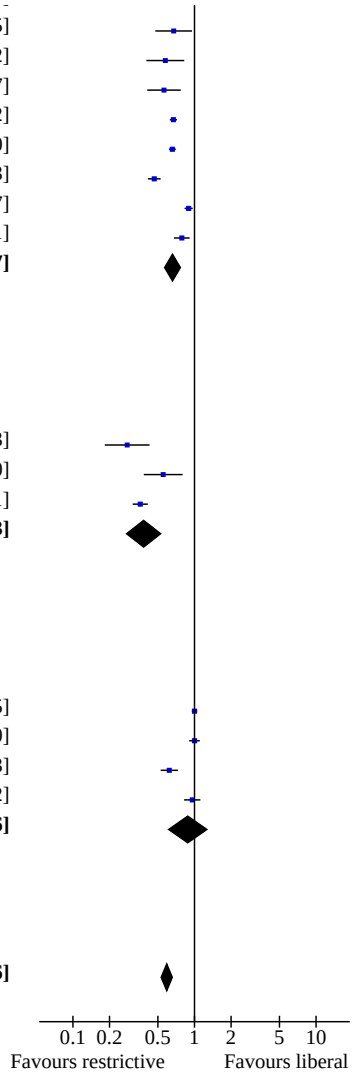
Analysis 6.2. (Continued)

de Almeida 2015	33	101	47	97	2.2%	0.67 [0.48 , 0.95]
Gobatto 2019	13	23	21	21	2.2%	0.58 [0.40 , 0.82]
Hébert 1995	18	33	35	36	2.3%	0.56 [0.41 , 0.77]
Hébert 1999	280	418	420	420	2.9%	0.67 [0.63 , 0.72]
Holst 2014	326	502	490	496	2.9%	0.66 [0.62 , 0.70]
Lacroix 2007	146	320	310	317	2.8%	0.47 [0.41 , 0.53]
Palmieri 2017	141	168	166	177	2.9%	0.89 [0.83 , 0.97]
Walsh 2013	40	51	49	49	2.7%	0.79 [0.68 , 0.91]
Subtotal (95% CI)		**1767**		**1762**	**23.3%**	**0.66 [0.57 , 0.77]**
Total events:	1059		1629			
Heterogeneity: Tau² = 0.04; Chi² = 105.22, df = 8 (P < 0.00001); I² = 92%						
Test for overall effect: Z = 5.48 (P < 0.00001)						
6.2.6 Acute myocardial infarction						
Carson 2013	15	55	55	55	2.0%	0.28 [0.18 , 0.43]
Cooper 2011	13	24	21	21	2.1%	0.55 [0.38 , 0.80]
Ducrocq 2021	122	342	323	324	2.7%	0.36 [0.31 , 0.41]
Subtotal (95% CI)		**421**		**400**	**6.8%**	**0.38 [0.28 , 0.53]**
Total events:	150		399			
Heterogeneity: Tau² = 0.06; Chi² = 6.68, df = 2 (P = 0.04); I² = 70%						
Test for overall effect: Z = 5.88 (P < 0.00001)						
6.2.7 Haematological malignancies						
DeZern 2016	59	59	30	30	2.9%	1.00 [0.95 , 1.05]
Stanworth 2020	20	20	18	18	2.8%	1.00 [0.91 , 1.10]
Tay 2020	80	150	129	150	2.7%	0.62 [0.53 , 0.73]
Webert 2008	26	29	29	31	2.7%	0.96 [0.82 , 1.12]
Subtotal (95% CI)		**258**		**229**	**11.1%**	**0.88 [0.61 , 1.26]**
Total events:	185		206			
Heterogeneity: Tau² = 0.13; Chi² = 145.03, df = 3 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**9957**		**10020**	**100.0%**	**0.59 [0.53 , 0.66]**
Total events:	4949		8168			
Heterogeneity: Tau² = 0.10; Chi² = 1104.74, df = 40 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 9.82 (P < 0.00001)						
Test for subgroup differences: Chi² = 25.21, df = 6 (P = 0.0003), I² = 76.2%						



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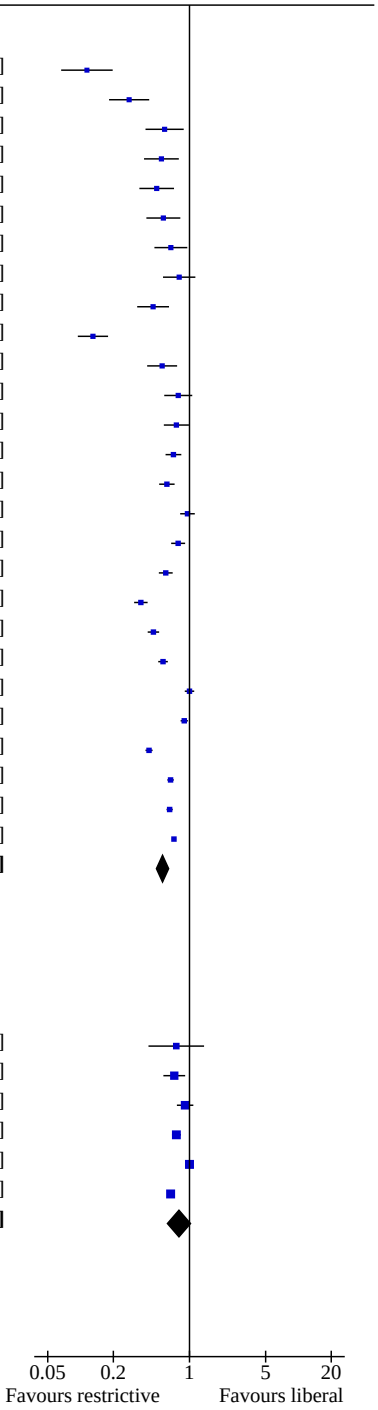
Analysis 6.3. Comparison 6: Blood transfusions, Outcome 3: Participants exposed to blood transfusion (by transfusion threshold)

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Difference between liberal and restrictive haemoglobin thresholds ≥ 2.0 g/dL						
Parker 2013	11	100	100	100	2.4%	0.11 [0.07 , 0.20]
Carson 2013	15	55	55	55	2.9%	0.28 [0.18 , 0.43]
Shehata 2012	13	25	22	25	3.0%	0.59 [0.39 , 0.88]
Cooper 2011	13	24	21	21	3.2%	0.55 [0.38 , 0.80]
Foss 2009	22	60	44	60	3.2%	0.50 [0.35 , 0.72]
Gobatto 2019	13	23	21	21	3.2%	0.58 [0.40 , 0.82]
de Almeida 2015	33	101	47	97	3.3%	0.67 [0.48 , 0.95]
Grover 2006	37	109	46	109	3.3%	0.80 [0.57 , 1.13]
Carson 1998	19	42	41	42	3.3%	0.46 [0.33 , 0.65]
Prick 2014	33	261	251	258	3.4%	0.13 [0.09 , 0.18]
Hébert 1995	18	33	35	36	3.4%	0.56 [0.41 , 0.77]
Fan 2014	41	96	52	96	3.5%	0.79 [0.59 , 1.06]
Johnson 1992	15	20	18	18	3.6%	0.76 [0.58 , 0.99]
Jairath 2015	133	403	247	533	4.0%	0.71 [0.60 , 0.84]
Tay 2020	80	150	129	150	4.0%	0.62 [0.53 , 0.73]
Webert 2008	26	29	29	31	4.1%	0.96 [0.82 , 1.12]
Walsh 2013	40	51	49	49	4.1%	0.79 [0.68 , 0.91]
Hajjar 2010	118	249	198	253	4.1%	0.61 [0.52 , 0.70]
Ducrocq 2021	122	342	323	324	4.1%	0.36 [0.31 , 0.41]
Lacroix 2007	146	320	310	317	4.1%	0.47 [0.41 , 0.53]
Villanueva 2013	219	444	384	445	4.2%	0.57 [0.52 , 0.63]
Stanworth 2020	20	20	18	18	4.2%	1.00 [0.91 , 1.10]
Palmieri 2017	141	168	166	177	4.2%	0.89 [0.83 , 0.97]
Carson 2011	415	1009	974	1007	4.2%	0.43 [0.39 , 0.46]
Hébert 1999	280	418	420	420	4.3%	0.67 [0.63 , 0.72]
Holst 2014	326	502	490	496	4.3%	0.66 [0.62 , 0.70]
Mazer 2017	1271	2430	1765	2430	4.3%	0.72 [0.69 , 0.75]
Subtotal (95% CI)		**7484**		**7588**	**100.0%**	**0.57 [0.50 , 0.64]**
Total events:	3620		6255			
Heterogeneity: Tau² = 0.10; Chi² = 680.60, df = 26 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 8.68 (P < 0.00001)						
6.3.2 Difference between liberal and restrictive haemoglobin thresholds < 2.0 g/dL						
Nielsen 2014	11	30	16	33	9.1%	0.76 [0.42 , 1.36]
Bracey 1999	74	212	104	216	16.4%	0.72 [0.58 , 0.91]
Bush 1997	40	50	43	49	17.5%	0.91 [0.77 , 1.08]
Gregersen 2015	109	144	140	140	18.7%	0.76 [0.69 , 0.83]
DeZern 2016	59	59	30	30	19.1%	1.00 [0.95 , 1.05]
Murphy 2015	637	1000	952	1003	19.1%	0.67 [0.64 , 0.70]
Subtotal (95% CI)		**1495**		**1471**	**100.0%**	**0.80 [0.63 , 1.02]**
Total events:	930		1285			
Heterogeneity: Tau² = 0.08; Chi² = 198.53, df = 5 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 1.79 (P = 0.07)						
Test for subgroup differences: Chi² = 6.11, df = 1 (P = 0.01), I² = 83.6%						



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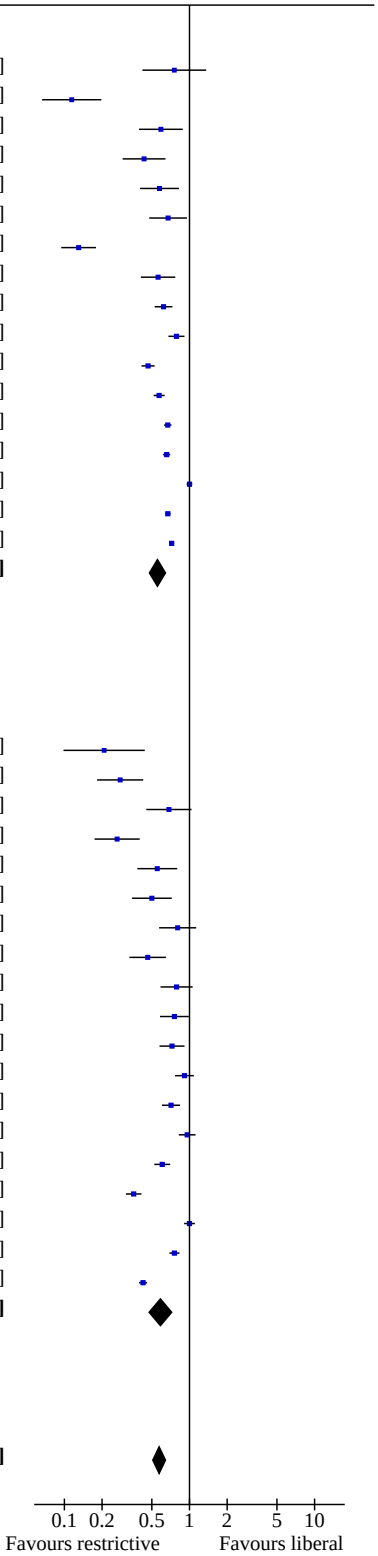
Analysis 6.4. Comparison 6: Blood transfusions, Outcome 4: Participants exposed to blood transfusion by transfusion threshold

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 Restrictive 7.0 g/dL to 7.5 g/dL						
Nielsen 2014	11	30	16	33	1.8%	0.76 [0.42 , 1.36]
Parker 2013	11	100	100	100	1.9%	0.11 [0.07 , 0.20]
Shehata 2012	13	25	22	25	2.4%	0.59 [0.39 , 0.88]
Gillies 2020	15	36	25	26	2.4%	0.43 [0.29 , 0.64]
Gobatto 2019	13	23	21	21	2.5%	0.58 [0.40 , 0.82]
de Almeida 2015	33	101	47	97	2.5%	0.67 [0.48 , 0.95]
Prick 2014	33	261	251	258	2.6%	0.13 [0.09 , 0.18]
Hébert 1995	18	33	35	36	2.7%	0.56 [0.41 , 0.77]
Tay 2020	80	150	129	150	3.1%	0.62 [0.53 , 0.73]
Walsh 2013	40	51	49	49	3.1%	0.79 [0.68 , 0.91]
Lacroix 2007	146	320	310	317	3.2%	0.47 [0.41 , 0.53]
Villanueva 2013	219	444	384	445	3.2%	0.57 [0.52 , 0.63]
Hébert 1999	280	418	420	420	3.3%	0.67 [0.63 , 0.72]
Holst 2014	326	502	490	496	3.3%	0.66 [0.62 , 0.70]
DeZern 2016	59	59	30	30	3.3%	1.00 [0.95 , 1.05]
Murphy 2015	637	1000	952	1003	3.3%	0.67 [0.64 , 0.70]
Mazer 2017	1271	2430	1765	2430	3.3%	0.72 [0.69 , 0.75]
Subtotal (95% CI)		**5983**		**5936**	**47.8%**	**0.55 [0.48 , 0.64]**
Total events:	3205		5046			
Heterogeneity: Tau² = 0.08; Chi² = 541.03, df = 16 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 7.82 (P < 0.00001)						
6.4.2 Restrictive < 8.0 g/dL to 9.0 g/dL						
Blair 1986	5	26	24	24	1.4%	0.21 [0.10 , 0.44]
Carson 2013	15	55	55	55	2.3%	0.28 [0.18 , 0.43]
Topley 1956	8	12	10	10	2.3%	0.68 [0.45 , 1.04]
Lotke 1999	16	62	65	65	2.3%	0.26 [0.17 , 0.40]
Cooper 2011	13	24	21	21	2.5%	0.55 [0.38 , 0.80]
Foss 2009	22	60	44	60	2.5%	0.50 [0.35 , 0.72]
Grover 2006	37	109	46	109	2.6%	0.80 [0.57 , 1.13]
Carson 1998	19	42	41	42	2.6%	0.46 [0.33 , 0.65]
Fan 2014	41	96	52	96	2.7%	0.79 [0.59 , 1.06]
Johnson 1992	15	20	18	18	2.8%	0.76 [0.58 , 0.99]
Bracey 1999	74	212	104	216	2.9%	0.72 [0.58 , 0.91]
Bush 1997	40	50	43	49	3.1%	0.91 [0.77 , 1.08]
Jairath 2015	133	403	247	533	3.1%	0.71 [0.60 , 0.84]
Webert 2008	26	29	29	31	3.1%	0.96 [0.82 , 1.12]
Hajjar 2010	118	249	198	253	3.1%	0.61 [0.52 , 0.70]
Ducrocq 2021	122	342	323	324	3.1%	0.36 [0.31 , 0.41]
Stanworth 2020	20	20	18	18	3.2%	1.00 [0.91 , 1.10]
Gregersen 2015	109	144	140	140	3.2%	0.76 [0.69 , 0.83]
Carson 2011	415	1009	974	1007	3.3%	0.43 [0.39 , 0.46]
Subtotal (95% CI)		**2964**		**3071**	**52.2%**	**0.59 [0.48 , 0.72]**
Total events:	1248		2452			
Heterogeneity: Tau² = 0.19; Chi² = 458.25, df = 18 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 5.06 (P < 0.00001)						
Total (95% CI)		**8947**		**9007**	**100.0%**	**0.57 [0.51 , 0.64]**
Total events:	4453		7498			
Heterogeneity: Tau² = 0.11; Chi² = 1054.09, df = 35 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 9.41 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%						



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Analysis 6.4. (Continued)

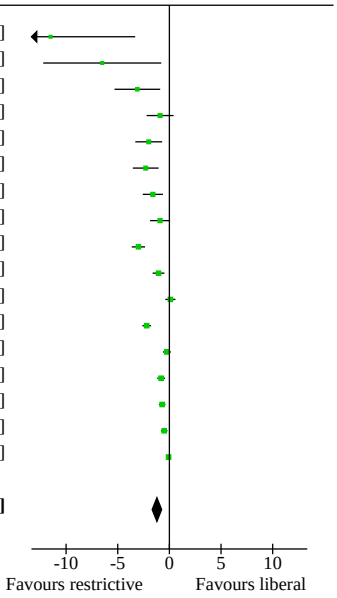
Test for overall effect: Z = 9.41 (P < 0.00001)
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%

Favours restrictive Favours liberal

Analysis 6.5. Comparison 6: Blood transfusions, Outcome 5: Units of blood transfused

Study or Subgroup	Restrictive Mean	SD	Total	Liberal Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Palmieri 2017	20.3	32.7	168	31.8	44.3	177	0.3%	-11.50 [-19.69 , -3.31]
Topley 1956	4.8	6.7	12	11.3	6.9	10	0.6%	-6.50 [-12.21 , -0.79]
DeZern 2016	8.2	4.2	59	11.3	5.4	30	2.8%	-3.10 [-5.31 , -0.89]
Bush 1997	2.8	3.1	50	3.7	3.5	49	4.9%	-0.90 [-2.20 , 0.40]
Blair 1986	2.6	3	26	4.6	1.5	24	5.0%	-2.00 [-3.30 , -0.70]
Tay 2020	2.73	4.81	150	5.02	6.13	150	5.1%	-2.29 [-3.54 , -1.04]
Gobatto 2019	1.5	1.7	23	3.1	1.6	21	6.0%	-1.60 [-2.58 , -0.62]
Cooper 2011	1.6	2	24	2.5	1.3	21	6.0%	-0.90 [-1.87 , 0.07]
Hébert 1999	2.6	4.1	418	5.6	5.3	420	7.1%	-3.00 [-3.64 , -2.36]
Johnson 1992	1	0.86	20	2.05	0.93	18	7.3%	-1.05 [-1.62 , -0.48]
Ducrocq 2021	2.9	3.7	342	2.8	2.7	324	7.5%	0.10 [-0.39 , 0.59]
Villanueva 2013	1.5	2.3	444	3.7	3.8	445	7.7%	-2.20 [-2.61 , -1.79]
Kola 2020	1.72	1.38	112	1.96	1.54	112	7.8%	-0.24 [-0.62 , 0.14]
Lacroix 2007	0.9	2.6	320	1.7	2.2	317	7.8%	-0.80 [-1.17 , -0.43]
Jairath 2015	1.2	2.1	403	1.9	2.8	533	7.9%	-0.70 [-1.01 , -0.39]
Bracey 1999	0.9	1.5	212	1.4	1.8	216	7.9%	-0.50 [-0.81 , -0.19]
So-Osman 2013	0.78	1.4	299	0.86	1.6	304	8.1%	-0.08 [-0.32 , 0.16]
Total (95% CI)			**3082**			**3171**	**100.0%**	**-1.21 [-1.67 , -0.75]**

Heterogeneity: Tau² = 0.66; Chi² = 173.58, df = 16 (P < 0.00001); I² = 91%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Not applicable



Comparison 7. Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Myocardial infarction	8	8219	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]
7.2 Renal failure	7	9198	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.28]
7.3 Infection	8	9219	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.79, 1.28]
7.4 Congestive heart failure	4	858	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.24, 2.43]
7.5 Thromboembolism	3	239	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.11, 9.55]
7.6 Cerebrovascular accident	4	905	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.22, 4.26]

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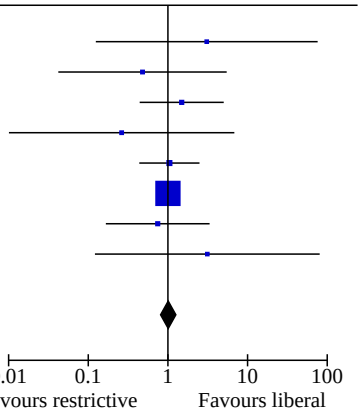
Analysis 7.1. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 1: Myocardial infarction

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bracey 1999	1	212	0	216	0.3%	3.07 [0.12 , 75.81]
Bush 1997	1	50	2	49	1.3%	0.48 [0.04 , 5.47]
Carson 2013	7	54	5	55	2.7%	1.49 [0.44 , 5.02]
Cooper 2011	0	23	1	19	1.0%	0.26 [0.01 , 6.82]
Ducrocq 2021	11	342	10	324	6.3%	1.04 [0.44 , 2.49]
Mazer 2017	144	2428	144	2429	85.6%	1.00 [0.79 , 1.27]
Murphy 2015	3	987	4	981	2.5%	0.74 [0.17 , 3.34]
Shehata 2012	1	25	0	25	0.3%	3.12 [0.12 , 80.39]
Total (95% CI)		**4121**		**4098**	**100.0%**	**1.01 [0.81 , 1.26]**
Total events:	168		166			

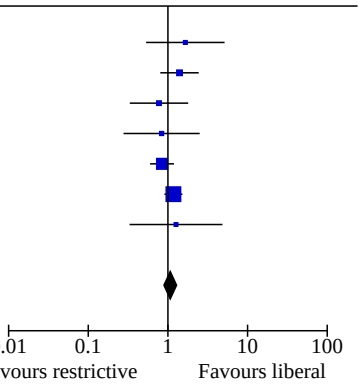
Heterogeneity: Chi² = 2.51, df = 7 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 2: Renal failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bracey 1999	8	212	5	216	2.1%	1.65 [0.53 , 5.14]
Ducrocq 2021	33	342	23	324	9.5%	1.40 [0.80 , 2.44]
Hajjar 2010	10	249	13	253	5.5%	0.77 [0.33 , 1.80]
Koch 2017	6	363	7	354	3.1%	0.83 [0.28 , 2.50]
Mazer 2017	61	2428	72	2429	31.3%	0.84 [0.60 , 1.19]
Murphy 2015	140	989	122	989	46.7%	1.17 [0.90 , 1.52]
Shehata 2012	6	25	5	25	1.7%	1.26 [0.33 , 4.84]
Total (95% CI)		**4608**		**4590**	**100.0%**	**1.07 [0.89 , 1.28]**
Total events:	264		247			

Heterogeneity: Chi² = 4.57, df = 6 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



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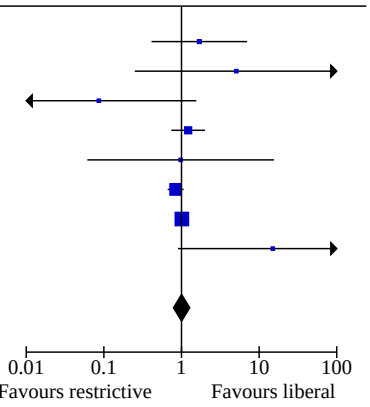
Analysis 7.3. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 3: Infection

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bracey 1999	5	212	3	216	2.7%	1.70 [0.41 , 7.02]
Carson 2013	2	54	0	55	0.6%	5.09 [0.25 , 103.64]
Ducrocq 2021	0	342	5	324	0.7%	0.09 [0.00 , 1.55]
Hajjar 2010	30	249	25	253	16.1%	1.22 [0.74 , 2.01]
Koch 2017	1	363	1	354	0.7%	0.98 [0.06 , 15.53]
Mazer 2017	121	2428	144	2429	35.1%	0.84 [0.66 , 1.06]
Murphy 2015	238	936	240	954	43.3%	1.01 [0.87 , 1.18]
Shehata 2012	7	25	0	25	0.7%	15.00 [0.90 , 249.30]
Total (95% CI)		**4609**		**4610**	**100.0%**	**1.00 [0.79 , 1.28]**
Total events:	404		418			

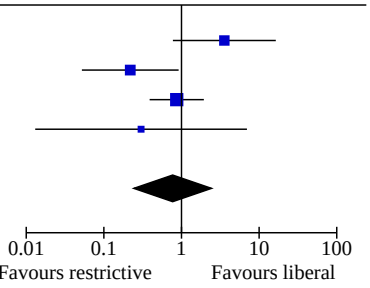
Heterogeneity: Tau² = 0.03; Chi² = 10.58, df = 7 (P = 0.16); I² = 34%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 4: Congestive heart failure

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2013	7	54	2	55	25.4%	3.56 [0.78 , 16.40]
Cooper 2011	2	24	8	21	26.8%	0.22 [0.05 , 0.92]
Ducrocq 2021	11	342	12	324	37.4%	0.87 [0.39 , 1.94]
Johnson 1992	0	20	1	18	10.4%	0.30 [0.01 , 6.97]
Total (95% CI)		**440**		**418**	**100.0%**	**0.77 [0.24 , 2.43]**
Total events:	20		23			

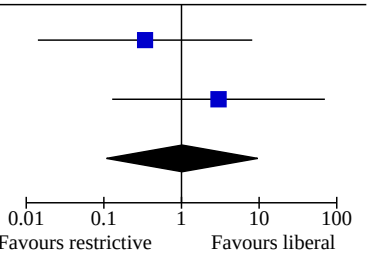
Heterogeneity: Tau² = 0.75; Chi² = 7.23, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 0.45 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 5: Thromboembolism

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Carson 2013	0	54	1	55	49.6%	0.34 [0.01 , 8.15]
Laine 2018	0	40	0	40		Not estimable
Shehata 2012	1	25	0	25	50.4%	3.00 [0.13 , 70.30]
Total (95% CI)		**119**		**120**	**100.0%**	**1.02 [0.11 , 9.55]**
Total events:	1		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable



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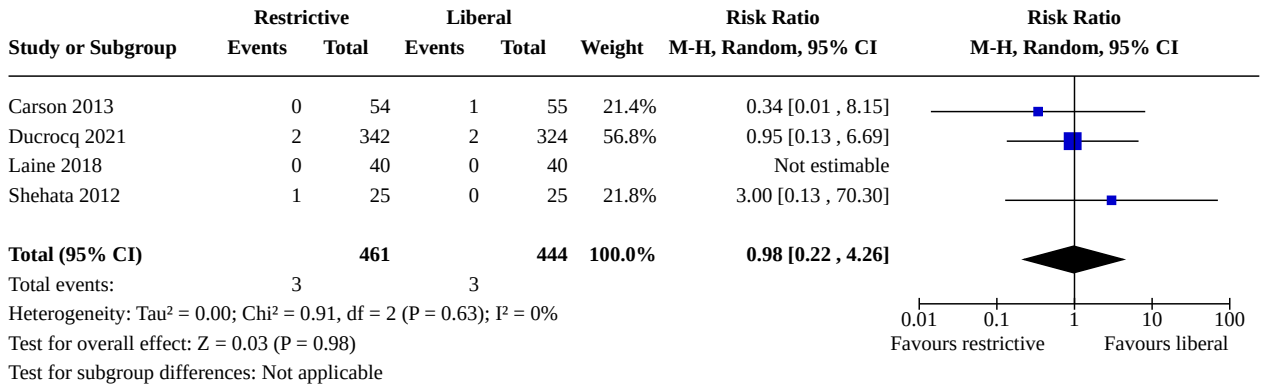
Analysis 7.6. Comparison 7: Morbidity outcomes in participants undergoing cardiac surgery or vascular surgery, and with acute MI, Outcome 6: Cerebrovascular accident



ADDITIONAL TABLES

Table 1. Trial setting details

Study ID	Number of participants at baseline	Country/Countries	Number of sites	Setting(s)	Year recruitment started
Mazer 2017	5092	19 countries[a]	73	73 sites - varied	2014
Carson 2011	2016	USA, Canada	47	47 sites - varied	2004
Murphy 2015	2003	UK	17	17 sites - varied	2009
Holst 2014	1005	Denmark, Sweden, Norway, Finland	32	32 general ICUs	2011
Jairath 2015	936	UK	6	University teaching hospitals	2012
Villanueva 2013	921	Spain	1	General hospital	2003
Hébert 1999	838	Canada	25	Tertiary (22), community ICU (3)	1994
Koch 2017	722	USA (1), India (1)	2	1 academic affiliated hospital in the USA, a private hospital in India	2007
Ducrocq 2021	668	France, Spain	35	35 sites - varied	2016
Lacroix 2007	648	Canada, Belgium, USA, UK	19	Tertiary paediatric ICU	2001
So-Osman 2013	603	Netherlands	3	Varied - university and general hospitals	2001
Prick 2014	519	Netherlands	37	Varied - university and general hospitals	2004
Hajjar 2010	512	Brazil	1	University teaching hospital	2009

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Table 1. Trial setting details *(Continued)*

Hoff 2011	466	Denmark	??	Oncology centres	1986
Bracey 1999	428	USA	1	University teaching hospital	1997
Palmieri 2017	345	US (16 sites), Canada (1), New Zealand (1)	18	Specialist burn centres	2010
Tay 2020	300	Canada	4	HCT sites	2011
Bergamin 2017	300	Brazil	1	University teaching hospital	2012
Gregersen 2015	284	Denmark	1	University teaching hospital	2010
Grover 2006	260	UK	3	Acute hospitals	Not stated
Kola 2020	224	India	1	Tertiary hospital	2015
Parker 2013	200	UK	1	General hospital	2002
de Almeida 2015	198	Brazil	1	Tertiary oncology university hospital	2012
Fan 2014	192	China	1	University teaching hospital	2011
Akyildiz 2018	180	Turkey	1	University teaching hospital	2014
Yakymenko 2018	133	Denmark	1	University teaching hospital	2010
Lotke 1999	127	USA	1	University teaching hospital	Not stated
Foss 2009	120	Denmark	1	University teaching hospital	2004
Carson 2013	110	USA	8	8 sites - varied	2010
Walsh 2013	100	UK	6	Varied - university and general hospitals	2009
Bush 1997	99	USA	1	University teaching hospital	1995
DeZern 2016	89	USA	1	Tertiary referral centre for oncology	2014
Carson 1998	84	USA (3), UK (1)	4	University teaching hospitals	1996
Laine 2018	80	Finland	1	University teaching hospital	2014
Hébert 1995	69	Canada	5	Tertiary hospitals	1993
Nielsen 2014	66	Denmark	2	University teaching hospital and general hospital	2009
Gillies 2020	62	UK	1	University teaching hospital	2017
Webert 2008	60	Canada	4	Tertiary oncology centres	2003
Møller 2019	58	Denmark	1	General hospital	2015

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Table 1. Trial setting details *(Continued)*

Shehata 2012	50	Canada	1	University teaching hospital	2007
Blair 1986	50	UK	1	University teaching hospital	Not stated
Gobatto 2019	47	Brazil	1	University teaching hospital	2014
Cooper 2011	45	USA	2	Veterans' Affairs hospital centres	2003
Johnson 1992	39	USA	1	University teaching hospital	Not stated
Stanworth 2020	38	UK, Australia, New Zealand	12	12 sites - varied	2015
Topley 1956	22	UK	1	'Accident hospital'	Not stated
Januarysen 2020	19	Netherlands	3	1 university hospital, 2 general hospitals	2002
Robitaille 2013	6	Canada	1	Not identified	2009

[a]Mazer 2017 (TRICS-III): majority of sites in USA; sites also in Australia, Brazil, Canada, China, Colombia, Denmark, Egypt, Germany, Greece, India, Israel, Malaysia, New Zealand, Romania, Singapore, South Africa, Spain, and Switzerland.

APPENDICES

Appendix 1. Search strategies 2011 (for 2012 update)

Cochrane Injuries Group's Specialised Register (searched 1 February 2011)

(Blood or "Red blood cell" or "Red blood cells" or RBC) and (therap* or transfus*) and (polic* or practice or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard* or restrict* or liberal* or management or program*)

Cochrane Central Register of Controlled Trials (CENTRAL; 2011, Issue 1), in the Cochrane Library

#1 MeSH descriptor Blood Transfusion, this term only with qualifiers: MT,ST
#2 transfus* near5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)
#3 (Red blood cell* or RBC) near5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*) and (therap* or transfus*)
#4 (H?emoglobin or h?emocrit or HB or HCT) near5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)
#5 transfus* near5 (restrict* or liberal*)
#6 (blood transfus*) near3 (management or program*)
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

MEDLINE (Ovid) 1948 to January Week 3 2011

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
3. 1 or 2
4. exp Reference Standards/
5. standards.fs.
6. methods.fs.
7. 4 or 5 or 6
8. 3 and 7
9. (transfus* adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.
10. ((Red blood cell* or RBC) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.
11. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.

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12. (transfus* adj5 (restrict* or liberal*)).mp.
13. ((blood or transfus*) adj3 (management or program*)).mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. randomi?ed.ab,ti.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. placebo.ab.
19. clinical trials as topic.sh.
20. randomly.ab.
21. trial.ti.
22.15 or 16 or 17 or 18 or 19 or 20 or 21
23. (animals not (humans and animals)).sh.
24. 22 not 23
25. 24 and 14

Embase (Ovid) 1980 to Week 4 2011

1. *Blood Transfusion/
2. ((Red blood cell* or RBC) adj3 (therap* or transfus*)).mp.
3. 1 or 2
4. exp standard/
5. 3 and 4
6. (transfus* adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.
7. ((Red blood cell* or RBC) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.
8. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard*)).mp.
9. (transfus* adj5 (restrict* or liberal*)).mp.
10. ((blood or transfus*) adj3 (management or program*)).mp.
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp Randomized Controlled Trial/
13. exp controlled clinical trial/
14. randomi?ed.ab,ti.
15. placebo.ab.
16. *Clinical Trial/
17. randomly.ab.
18. trial.ti.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animal/ not (exp human/ and exp animal/)
21. 19 not 20
22. 11 and 21

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to February 2011) and ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to February 2011)

#1 TS=((Blood or "Red blood cell" or "Red blood cells" or RBC or Hemoglobin* or haemoglobin* or haemocrit or hemocrit or HB or HCT) SAME transfus*)
#2 TS=(polic* or practice or protocol* or trigger* or threshold* or indicator* or strateg* or criteri* or standard* or restrict* or liberal* or management or program*)
#3 #1 and #2
#4 TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
#5 TS=((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))
#6 #2 or #3
#7 #3 and #6
#8 Topic=(human*)
#9 #7 and #8

Appendix 2. Search strategies May 2016

CENTRAL, in the Cochrane Library
#1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD]
#2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST]

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#3 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) near/5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*))
#4 ((h?emoglobin or h?ematocrit or HB or HCT) near/5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*))
#5 (blood near/3 (management or program*))
#6 ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)):ti
#7 #1 or #2 or #3 or #4 or #5 or #6

MEDLINE (OvidSP) 1. *Blood Transfusion/ad, mt, st, td or *Erythrocyte Transfusion/mt, st, td
2. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).tw.
3. ((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).tw.
4. (blood adj3 (management or program*)).mp.
5. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)).ti.
6. or/1-5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomi*.tw.
10. placebo.ab.
11. clinical trials as topic.sh.
12. randomly.ab.
13. groups.ab.
14. trial.tw.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans/
17. 15 not 16
18. 6 and 17

Embase (OvidSP) 1. *Blood Transfusion/ or Erythocyte Transfusion/
2. ((red blood cell* or red cell* or RBC* or PRBC*) adj5 (therap* or transfus*)).mp.
3. 1 or 2
4. Standard/ or Gold Standard/
5. 3 and 4
6. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).tw.
7. ((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).tw.
8. (blood adj3 (management or program*)).mp.
9. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)).ti.
10. or/5-9
11. Randomized Controlled Trial/
12. Randomization/
13. Single Blind Procedure/
14. Double Blind Procedure/
15. Crossover Procedure/
16. Placebo/
17. exp Clinical Trial/
18. Prospective Study/
19. (randomi* or double-blind* or single-blind* or RCT*).tw.
20. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
21. (crossover* or cross over* or cross-over* or placebo*).tw.
22. ((treble or triple) adj blind*).tw.
23. or/11-22
24. Case Study/
25. case report*.tw.
26. (note or editorial).pt.
27. or/24-26
28. 23 not 27

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29. limit 28 to embase
30. 10 and 29

PubMed (for E-publications ahead of print only)
#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))
#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))
#3 (blood[TI] AND (management[TI] OR program*[TI]))
#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4
#6 (random* OR blind* OR "control group" OR placebo* OR controlled 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])
#7 #5 AND #6

Transfusion Evidence Library
Subject Area: Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme)
OR
Subject Area: Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

Web of Science Conference Proceedings Citation Index - Science (CPCI-S) ((TOPIC: ((transfus* OR "red cell*" OR "red blood cell*" OR RBC* OR PRBC*) NEAR/5 (trigger* OR threshold* OR target* OR restrict* OR liberal* OR aggressive* OR conservative* OR prophylactic* OR limit* OR protocol* OR policy OR policies OR practic* OR indicat* OR strateg* OR regimen* OR criteri* OR standard* OR management OR program*)) OR (TOPIC: ((hemoglobin OR haemoglobin OR hematocrit OR haematocrit OR HB OR HCT) NEAR/5 (polic* OR practic* OR protocol* OR trigger* OR threshold* OR maintain* OR indicator* OR strateg* OR criteri* OR standard*))) OR (TOPIC: (blood NEAR/3 (management OR program*))) AND (TOPIC: (random* OR blind* OR "control group" OR placebo* OR "controlled trial" OR "controlled study" OR "controlled clinical trial" OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR "literature search" OR medline OR cochrane OR embase))

Appendix 3. Search strategies ongoing trial registries May 2016

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and ***World Health Organization International Clinical Trials Registry Platform(ICTRP)***

Title/Intervention= *(*transfusion and (liberal or restrictive or threshold or Hb or haemoglobin or hemoglobin or haemaglobin or hemaglobin))

We also conducted an earlier search on the international trial registries in December 2015.

US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov
INFLECT EXACT "Interventional" [STUDY-TYPES] AND ("blood transfusion" OR "hemoglobin threshold" OR "haemoglobin threshold" OR "red blood cell transfusion") [TREATMENT] AND ("01/02/2011": "12/09/2015") [FIRST-RECEIVED-DATE]

World Health Organization International Clinical Trials Registry Platform (ICTRP)
Intervention: "blood transfusion" OR "red blood cell transfusion" OR "hemoglobin threshold" OR "haemoglobin threshold"
Recruitment status: ALL
Date of registration: 01/02/2011 to 09/12/2015

ISRCTN Registry
Intervention: "blood transfusion"
Date applied: 01/02/2011 to 09/12/2015

Appendix 4. Search strategies 2020 (for 2021 update)

CENTRAL
#1 MeSH descriptor: [Blood Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST, Trends - TD]
#2 MeSH descriptor: [Erythrocyte Transfusion] this term only and with qualifier(s): [Methods - MT, Standards - ST]

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#3 ((transfus* OR "red cell" OR "red cells" OR "red blood cell" OR "red blood cells" OR RBC* OR PRBC*) and (trigger* OR thresh?old* OR target* OR restrict* OR liberal* OR aggressive* OR conservative* OR prophylactic* OR limit* OR protocol* OR policy OR policies OR practic* OR indicat* OR strateg* OR regimen* OR criteri* OR standard* OR management OR program*)):ti,ab
#4 ((h?emoglobin OR h?ematocrit OR HB OR HCT) and (polic* OR practic* OR protocol* OR trigger* OR threshold* OR maintain* OR indicator* OR strateg* OR criteri* OR standard*)):ti
#5 (blood near/3 (management OR program*)):ti
#6 ((transfus* OR "red cell" OR "red cells" OR "red blood cell" OR "red blood cells" OR RBC* OR PRBC*) and (critical* OR intensive* OR h?emorrhag* OR bleed*)):ti
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

MEDLINE
1. *Blood Transfusion/ad, mt, st, td or *Erythrocyte Transfusion/mt, st, td
2. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).tw.
3. ((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).tw.
4. (blood adj3 (management or program*)).mp.
5. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)).ti.
6. or/1-5
7. (Randomized Controlled Trial or Controlled Clinical Trial or Clinical Trial Protocol).pt.
8. (randomi* or randomly or placebo).tw,kf.
9. trial.ti,kf.
10. Clinical Trials as Topic/
11. Clinical Trial, Phase III/ or ("phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kf.
12. or/7-11
13. (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/
14. 12 not 12
15. 6 and 14

Embase
1. *Blood Transfusion/ or Erythocyte Transfusion/
2. ((red blood cell* or red cell* or RBC* or PRBC*) adj5 (therap* or transfus*)).mp.
3. 1 or 2
4. Standard/ or Gold Standard/
5. 3 and 4
6. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).tw.
7. ((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).tw.
8. (blood adj3 (management or program*)).mp.
9. ((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)).ti.
10. or/5-9
11. crossover-procedure/ or double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/
12. (random* or factorial* or crossover* or (cross adj1 over*) or placebo* or (doubl* adj1 blind*) or (singl* adj1 blind*) or assign* or allocat* or volunteer*).tw.
13. 11 or 12
14. (animal* or cat or cats or dog or dogs or pig or pigs or sheep or rabbit* or mouse or mice or rat or rats or feline or canine or porcine or ovine or murine or model*).ti.
15. 13 not 14
16. 10 and 15
17. limit 16 to (conference abstracts or embase)

PubMed
#1 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*) AND (trigger*[TI] OR threshold*[TI] OR target*[TI] OR restrict*[TI] OR liberal*[TI] OR aggressive*[TI] OR conservative*[TI] OR prophylactic*[TI] OR limit*[TI] OR protocol*[TI] OR policy[TI] OR policies[TI] OR practic*[TI] OR indicat*[TI] OR strateg*[TI] OR regimen*[TI] OR criteri*[TI] OR standard*[TI] OR management[TI] OR program*[TI]))
#2 ((hemoglobin[TI] OR haemoglobin[TI] OR hematocrit[TI] OR haematocrit[TI] OR HB[TI] OR HCT[TI]) AND (polic*[TI] OR practic*[TI] OR protocol*[TI] OR trigger*[TI] OR threshold*[TI] OR maintain*[TI] OR indicator*[TI] OR strateg*[TI] OR criteri*[TI] OR standard*[TI]))
#3 (blood[TI] AND (management[TI] OR program*[TI]))

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#4 ((transfus*[TI] OR red cell*[TI] OR red blood cell*[TI] OR RBC*[TI] OR PRBC*[TI]) and (critical*[TI] OR intensive*[TI] OR hemorrhag*[TI] OR haemorrhage*[TI] OR bleed*[TI]))
#5 #1 OR #2 OR #3 OR #4
#6 (random* OR blind* OR "control group" OR placebo* OR controlled 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])
#7 #5 AND #6

TRANSFUSION EVIDENCE LIBRARY
Subject Area: Red Cells AND (trigger OR threshold OR target OR restrict OR restrictive OR liberal OR aggressive OR aggressively OR conservative OR prophylactic OR limit OR limits OR protocol OR policy OR policies OR practice OR indicator OR strategy OR strategies OR regimen OR criteria OR standard OR management OR program OR programme)
OR
Subject Area: Red Cells AND title:(critical OR critically OR intensive OR intensively OR hemorrhage OR haemorrhage OR hemorrhaging OR haemorrhaging OR bleed OR bleeding)

WEB OF SCIENCE - Conference Proceedings Citation Index - Science (CPCI-S)
#1 TS=((transfus* OR "red cell*" OR "red blood cell*" OR RBC* OR PRBC*) NEAR/5 (trigger* OR threshold* OR target* OR restrict* OR liberal* OR aggressive* OR conservative* OR prophylactic* OR limit* OR protocol* OR policy OR policies OR practic* OR indicat* OR strateg* OR regimen* OR criteri* OR standard* OR management OR program*))
#2 TS=((hemoglobin OR haemoglobin OR hematocrit OR haematocrit OR HB OR HCT) NEAR/5 (polic* OR practic* OR protocol* OR trigger* OR threshold* OR maintain* OR indicator* OR strateg* OR criteri* OR standard*))
#3 TS= (blood NEAR/3 (management OR program*))
#4 #1 OR #2 OR #3
#5 TS=(random* OR blind* OR "control group" OR placebo* OR "controlled trial" OR "controlled study" OR "controlled clinical trial" OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR "literature search" OR medline OR cochrane OR embase)
#6 #4 AND #5

ClinicalTrials.gov
Other Terms: trigger OR threshold OR target OR restrict OR liberal OR aggressive OR conservative OR prophylactic OR limit OR protocol
Intervention: blood transfusion OR red cell transfusion OR RBC transfusion OR red blood cell transfusion
WHO ICTRP
transfusion AND trigger OR transfusion AND triggers OR transfusion AND threshold OR transfusion AND thresholds OR transfusion AND restrictive OR transfusion AND liberal OR transfusion AND aggressive OR transfusion AND conservative OR transfusion AND prophylactic OR transfusion protocol OR transfusion protocols
OR
transfusions AND trigger OR transfusions AND triggers OR transfusions AND threshold OR transfusions AND thresholds OR transfusions AND restrictive OR transfusions AND liberal OR transfusions AND aggressive OR transfusions AND conservative OR transfusions AND prophylactic OR transfusions protocol OR transfusions protocols

WHAT'S NEW

Date	Event	Description
25 January 2022	Amended	Typographical errors corrected

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2002

Date	Event	Description
16 December 2021	New search has been performed	The review has been updated to 16 November 2020. Two new review authors joined the team: Marialena Trivella in November 2020, and Jane Dennis in July 2021.

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Date	Event	Description
16 December 2021	New citation required and conclusions have changed	Update of 2016 review; 17 new trials are included. We added six-month (long-term) mortality as an outcome and clarified the outcome "blood transfusion as a measure of implementation".
13 November 2017	New search has been performed	We updated the search - the review was published elsewhere.
27 May 2016	New citation required and conclusions have changed	The conclusions of the review changed; the search date is now 27 May 2016.
26 May 2016	New search has been performed	We made the following changes • We added 16 new trials • We used 30-day mortality as the primary outcome because mortality is a more clinically relevant outcome and the number of participants enrolled in the trials provided sufficient power to examine this outcome • We added sensitivity analyses to evaluate heterogeneity for transfusion outcomes between trials • We made changes to the author line
20 December 2011	New citation required and conclusions have changed	We updated searches to February 2011. We included data from two new trials and amended the results accordingly. We identified one trial through the updated search; the other was previously included as an ongoing trial, and the results became available recently. We updated the Background section of the review. The overall conclusions of the review remain similar, but we have extended the clinical specialties for which the results can be generalised. As part of this update, we replaced the assessment of methodological quality used in earlier versions of this review with an assessment of risk of bias. This amendment is in accordance with a change in Cochrane's methodological guidance. The authors of the review have changed.
1 February 2011	New search has been performed	We updated the search for studies to February 2011.
9 September 2008	Amended	We converted the review to new review format.
17 November 2004	New search has been performed	We conducted an updated search for new trials in November 2004. We identified no new trials eligible for inclusion.

CONTRIBUTIONS OF AUTHORS

For the 2021 update

Carson, Stanworth and Dennis contributed equally to this review update. Carson and Stanworth continue to provide overall leadership of the review updates with clinical input; they screened abstracts and titles identified in the searches, and applied inclusion and exclusion criteria. Carson, Stanworth and Dennis extracted data, and assessed risk of bias of trials. Carson entered the data into Review Manager 5.4 and, with Trivella and Dennis, performed the initial analyses. Dennis and Trivella provided methodological and statistical input and assurance (Review Manager 5a). Stanworth and Carson prepared the first draft of the manuscript. Nareg Roubinian reviewed the accuracy of data and assisted with preparation of the manuscript. Fergusson provided methodological and statistical expertise and assisted with final drafts of the of the manuscript. Triulzi and Hébert reviewed the manuscript and provided content expertise. Doree performed additional literature searches.

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For the 2016 update

Carson and Stanworth screened abstracts and titles identified in the searches, applied inclusion and exclusion criteria, and assessed the quality of trials. Stanworth led the quality review, and Carson entered the data into Review Manager 5.3, performed initial analyses, and prepared the first draft of the manuscript (Review Manager 5a). Roubinian checked the accuracy of data and assisted with preparation of the manuscript. Fergusson provided methodological and statistical expertise and assisted with preparation of the manuscript. Triulzi and Hébert reviewed the manuscript and provided content expertise. Doree performed additional literature searches.

For the 2012 review

Paul Carless performed original database literature searches, screened abstracts and titles for relevant articles, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers, extracted data from trials, quality-assessed trials, entered data into Meta-View 4.1, entered all study details into Review Manager 5.1, and co-wrote the review (Review Manager 5b). Jeffrey Carson screened abstracts and titles for relevant articles, obtained relevant papers, applied inclusion/exclusion criteria to retrieved papers, extracted data from trials, quality-assessed trials, entered data and all study details into Review Manager 5.1, and co-wrote the review. Paul Hébert reviewed the manuscript and provided expertise with analysis and content expert opinion.

DECLARATIONS OF INTEREST

We have considered disclosures relevant to this review.

Jeffrey Carson reports being the chief investigator on three trials included in this review (Carson 1998; Carson 2011 (FOCUS); Carson 2013). He has received multiple grants supporting his institution from the US National Institutes of Health. He has been involved with guideline development for red cell transfusions in the Association for the Advancement of Blood & Biotherapies (AABB). He has received a grant from the US National Institutes of Health to evaluate transfusion thresholds in patients with acute myocardial infarction in an ongoing trial (MINT - NCT02981407).

Carolyn Dorée: nothing to declare.

Dean Fergusson reports being an author on three completed trials included within this review (Hébert 1999; Mazer 2017 (TRICS III); Shehata 2012). He was a Co-Principal Investigator on the TRICSIII trial (Mazer 2017); he is a member of the Steering Committee for the ongoing MINT trial (NCT02981407).

Paul Hébert reports being an author on three completed trials identified in this review (Hébert 1995; Hébert 1999; Lacroix 2007 (TRIPICU). He is the lead investigator on the study NCT02619136, the Canadian pilot study for MINT (NCT02981407, for which he is a member of the Executive Committee); he has published six non-Cochrane reviews in this area. He serves on a guideline panel for the American College of Chest Physicians (ACCP) and has written several editorials for leading journals concerning transfusion triggers.

Nareg Roubinian: nothing to declare.

Simon Stanworth reports being the chief investigator on one trial included in this review (Stanworth 2020); a coauthor on another (Gillies 2020 (RESULT-NOF)); and is a co-investigator on four ongoing trials (ISRCTN17438123; ACTRN12619001053112; NCT03871244; Morton 2020). He has received funding for four RBC transfusion trials, including three in patients with haematological malignancy. He has published three non-Cochrane reviews in this area.

Darrell Triulzi is a member of the Steering Committee for the ongoing MINT trial (NCT02981407) and a member of the scientific advisory board for Fresenius-Kabi.

Jane Dennis was employed by Cochrane Injuries during her involvement in development of the review.

Marialena Trivella was employed by Cochrane Injuries during her involvement in development of the review.

Data extraction for all trials was checked by NR. Final decisions on risk of bias assessments were made by review authors not involved in trials as researchers.

SOURCES OF SUPPORT

Internal sources

- National Institute for Health Research (NIHR), UK

  Provides support for the Cochrane Injuries Group, which employs authors MHT and JD

External sources

- No sources of support provided

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following differences were applied in this 2021 version of the review.

- We changed the title of the review from "Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion" to "Transfusion thresholds for guiding red blood cell transfusion".
- The authors of the review have changed - two new authors have been added (Marialena Trivella and Jane Dennis).
- We clarified the outcome of blood transfusion as a measure of treatment implementation and reported and analysed these elements more clearly.
- We added a new secondary outcome (transfusion-specific reactions).
- We added quality of life (QOL) to data items collected under 'function'.
- Our summary of findings table now reports on infections as a composite category, rather than 'pneumonia' as a specific one.
- We have added details of random-effects analysis into the data synthesis section.
- We no longer include an estimate of optimal information size (sample size calculations for trials to yield reliable information on mortality assuming baseline mortality at 30 days), given the breadth of clinical contexts included within this review.
- We have divided risk of bias assessment for outcome assessment by objective (mortality) and subjective (function, QOL) measures.
- We have omitted sensitivity analysis on the basis of outcome assessment for mortality, considering that the objective nature of the outcome makes blinding unimportant. Should future versions of the review include data suitable for meta-analysis for the outcomes of function and fatigue, we will conduct sensitivity analyses on the basis that blinding is relevant in such cases.
- We reviewed our ratings for bias under the domain of 'Selective outcome reporting'.

The following differences were applied in the 2016 version of the review.

- The primary outcome changed from "the proportion of patients 'at risk' who were transfused with red blood cells", to "30-day mortality". Previously, 30-day mortality was a secondary outcome. The proportion of participants 'at risk' who were transfused with red blood cells became a secondary outcome. The primary outcome was changed because mortality is a more clinically relevant outcome and the number of participants enrolled in trials provided sufficient power to examine this outcome.
- Sample size calculations that assumed a baseline 30-day mortality of 9% for restrictive transfusion, 90% power, alpha level of 0.05, indicated that to detect a 15%, 20%, or 25% relative decrease in mortality with the use of liberal transfusion, a trial would need to enrol 17,500, or 9600, or 6000 participants, respectively.
- We added one new exclusion criterion: we excluded trials that were not designed to include any clinical outcomes relevant to this review.
- We added a new sensitivity analysis: registered trials versus unregistered trials.
- We separated blinding of participants and personnel from blinding of outcome assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anemia [therapy]; *Erythrocyte Transfusion; Hematocrit; Hemoglobins; Prospective Studies; Randomized Controlled Trials as Topic

MeSH check words

Humans

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