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## **Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease (Review)**

Wilkinson KL, Brunskill SJ, Doree C, Trivella M, Gill R, Murphy MF

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Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease.

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[Intervention Review]

# Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

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## ABSTRACT

### Background

Congenital heart disease is the most commonly diagnosed neonatal congenital condition. Without surgery, only 30% to 40% of patients affected will survive to 10 years old. Mortality has fallen since the 1990s with 2006 to 2007 figures showing surgical survival at one year of 95%. Patients with congenital heart disease are potentially exposed to red cell transfusion at many points in the surgical pathway. There are a number of risks associated with red cell transfusion that may be translated into increased patient morbidity and mortality.

### Objectives

To evaluate the effects of red cell transfusion on mortality and morbidity on patients with congenital heart disease at the time of cardiac surgery.

### Search methods

We searched 11 bibliographic databases and three ongoing trials databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 5, 2013), MEDLINE (Ovid, 1950 to 11 June 2013), EMBASE (Ovid, 1980 to 11 June 2013), ClinicalTrials.gov, World Health Organization (WHO) ICTRP and the ISRCTN Register (to June 2013). We also searched references of all identified trials, relevant review articles and abstracts from between 2006 and 2010 of the most relevant conferences. We did not limit the searches by language of publication.

### Selection criteria

We included randomised controlled trials (RCTs) comparing red cell transfusion interventions in patients undergoing cardiac surgery for congenital heart disease. We included participants of any age (neonates, paediatrics and adults) and with any type of congenital heart disease (cyanotic or acyanotic). We excluded patients with congenital heart disease undergoing non-cardiac surgery. No co-morbidities were excluded.

### Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors for additional information.

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## Main results

We identified 11 trials (862 participants). All trials were in neonatal or paediatric populations. The trials covered only three areas of interest: restrictive versus liberal transfusion triggers (two trials), leukoreduction versus non-leukoreduction (two trials) and standard versus non-standard cardiopulmonary bypass (CPB) prime (seven trials). Owing to the clinical diversity in the participant groups (cyanotic (three trials), acyanotic (four trials) or mixed (four trials)) and the intervention groups, it was not appropriate to pool data in a meta-analysis. No study reported data for all the outcomes of interest to this review. Risk of bias was mixed across the included trials, with only attrition bias being low across all trials. Blinding of study personnel and participants was not always possible, depending on the intervention being used.

Five trials (628 participants) reported the primary outcome: 30-day mortality. In three trials (a trial evaluating restrictive and liberal transfusion (125 participants), a trial of cell salvage during CPB (309 participants) and a trial of washed red blood cells during CPB (128 participants)), there was no clear difference in mortality at 30 days between the intervention arms. In two trials comparing standard and non-standard CPB prime, there were no deaths in either randomised group. Long-term mortality was similar between randomised groups in one trial each comparing restrictive and liberal transfusion or standard and non-standard CPB prime.

Four trials explored a range of adverse effects following red cell transfusion. Kidney failure was the only adverse event that was significantly different: patients receiving cell salvaged red blood cells during CPB were less likely to have renal failure than patients not exposed to cell salvage (risk ratio (RR) 0.26, 95% confidence interval (CI) 0.09 to 0.79, 1 study, 309 participants). There was insufficient evidence to determine whether there was a difference between transfusion strategies for any other severe adverse events.

The duration of mechanical ventilation was measured in seven trials (768 participants). Overall, there was no consistent difference in the duration of mechanical ventilation between the intervention and control arms.

The duration of intensive care unit (ICU) stay was measured in six trials (459 participants). There was no clear difference in the duration of ICU stay between the intervention arms in the transfusion trigger and leukoreduction trials. In the standard versus non-standard CPB prime trials, one trial examining the impact of washing transfused bypass prime red blood cells showed no clear difference in duration of ICU stay between the intervention arms, while the trial assessing ultrafiltration of the priming blood showed a shorter duration of ICU stay in the ultrafiltration group.

## Authors' conclusions

There are only a small number of small and heterogeneous trials so there is insufficient evidence to assess the impact of red cell transfusion on patients with congenital heart disease undergoing cardiac surgery accurately. It is possible that the presence or absence of cyanosis impacts on trial outcomes, which would necessitate different clinical management of two groups. Further adequately powered, specific, high-quality trials are warranted to assess this fully.

## PLAIN LANGUAGE SUMMARY

### Blood transfusions in patients with heart problems requiring surgery on their heart

This review aims to determine the current evidence on the impact of red blood cell transfusion on patients born with heart problems undergoing heart surgery.

### Background

Between four and nine children out of every 1000 born alive have hearts that have not formed properly. Heart surgery may allow a child to live and grow or may correct the defect in children and adults alike. Patients often need red blood cell transfusions during or after heart surgery. Most patients will have the surgery on a cardiopulmonary bypass (CPB) machine, which acts as the heart and lungs during the operation. More patients are now surviving heart surgery and the aim is to make surgery even safer. Some research suggests that red blood cell transfusions may make people more ill.

### Study characteristics

We searched scientific sources to identify eligible trials and found 11 studies with 862 participants. We found no trials including adults. The identified studies examined three treatments: two trials compared giving a red blood cell transfusion only when the levels of haemoglobin in the blood fell below a certain concentration (known as a restrictive versus a liberal transfusion trigger); two trials compared whether there was a benefit to removing white blood cells (leukocytes) from the transfused red blood cells and seven trials

compared methods used to prepare the fluid for the CPB machine. The trials were different in terms of the age of the participants, the type of heart disease and the exact treatment studied so there was been no opportunity to pool data for analysis. All studies did not report on all outcomes (a measure of a participant's clinical and functional status that is used to assess the effectiveness of a treatment, e.g. death, side effects).

## Key results

Our primary outcome was death within 30 days after surgery. Five trials looked at this outcome and found no clear difference in mortality between the treatment arms. Four trials explored other adverse effects following a red blood cell transfusion. A difference in the number of adverse events was only observed for kidney failure: in one trial (with 309 participants), patients receiving cell salvaged red blood cells during CPB were less likely to have renal failure than patients not exposed to cell salvage.

## Quality of the evidence

This review identified only a few, small studies across three interventions. These studies measured many different aspects of red blood cell transfusion in patients having heart surgery so it is difficult to make accurate conclusions about the benefits or risks of red blood cell transfusion for these patients. More research is needed to allow accurate conclusions. Future studies should be bigger and focus on one aspect of transfusion in a specific type of heart disease.

# BACKGROUND

## Description of the condition

Congenital heart disease describes the presence of a structural abnormality of the heart present from birth (Bédard 2008), and more specifically a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance (Mitchell 1971). Although there is worldwide variation, primarily due to the ability to detect trivial lesions (Hoffman 2002), the estimated incidence is four to nine cases per 1000 live born infants (Dolk 2011; Perloff 2001). It is the most common congenital condition diagnosed in neonates (Gatzoulis 2005) with congenital heart defects accounting for 30% of all live born infants with a major congenital anomaly (EURO-PERISTAT project 2008). Neonates are born with a wide range of defects, for example, atrial and ventricular septal defects, transposition of the great arteries and tetralogy of Fallot (Bédard 2008).

The defects may be broadly classified into cyanotic or acyanotic heart disease. Cyanotic heart disease is caused by an increased amount of reduced haemoglobin (non-oxygenated blood) from either mixing of oxygenated and non-oxygenated blood (right to left shunting or univentricular heart) or inadequate pulmonary blood flow (underdeveloped pulmonary vasculature or progressive pulmonary hypertension). Examples of cyanotic lesions are transposition of the great arteries, truncus arteriosus and hypoplastic left heart syndrome. Acyanotic heart disease describes infants with normal oxygen levels (e.g. congenital aortic stenosis, atrioseptal defect, ventricular septal defect (Gatzoulis 2005)). Patients with

cyanotic heart disease have high haemoglobin and haematocrit levels and this has been shown to be a significant risk factor for perioperative bleeding and blood product use (Williams 1999).

Surgery for congenital heart disease aims to reduce mortality and morbidity. In the 1950s, without surgery, of 10 affected children born alive, two would die by the end of the first week, a further one or two by the end of the first month, with six in total having died by the end first year. Only three or four would survive to 10 years old (MacMahon 1953). Since this time, an improvement in diagnostic, interventional and surgical techniques has produced an overall dramatic decrease in mortality and morbidity rates (British Cardiac Society 2002). Between 1965 and 1975 in Canada, survival rates in the first month after surgery rose from 37% to 70% (Izukawa 1979). Between 1999 and 2006 in the US, overall mortality from congenital heart disease fell by 24.1% (Gilboa 2010). Surgical survival at one year in the UK was approximately 95% in 2006 to 2007 (CCAD 2008).

Patients present for surgery at a variable age according to the underlying defect but there are three main groups; neonates (within four weeks of birth), paediatrics (four weeks to 16 years) and adult congenital (over 16 years). The surgery may be either corrective (completely corrects the lesion into a normal circulation) or palliative (changes the anatomy/circulation into one that is more compatible with life). Whether the surgery is corrective or palliative depends on the underlying defect. Some patients will undergo a sequence of surgeries to correct their defects (e.g. patients with hypoplastic left heart syndrome) while other patients will need repeat operations. Almost half of adult congenital cardiac surgical operations are repeat operations (van der Bom 2011).

Mortality and morbidity are variable. For some defects (e.g. atrioseptal defects) surgery is relatively routine. For other defects, the patient is critically unwell and surgery has a very significant associated morbidity and mortality. Hypoplastic left heart syndrome is an example where children are often critically unwell at presentation and surgery has a significant mortality risk. These children will undergo a palliative three-stage repair throughout their early childhood. The first stage is the Norwood procedure where early mortality is estimated at 29% (McGuirk 2006). The second stage is the bidirectional Glenn procedure followed by the Fontan procedure (total cavopulmonary connection). One study in the US cited hypoplastic left heart syndrome as the greatest specific diagnosis contributor to overall congenital heart disease mortality at 10.9% of all deaths (Gilboa 2010).

More children are surviving after surgery for congenital heart disease with 80% to 85% expected to reach adulthood (Khairy 2010; Nieminen 2001; Wren 2001). Despite excellent outcomes for many individuals, challenges remain in all patient groups especially those at higher risk, such as neonates, premature infants and patients undergoing complex surgery (Cheng 2011; Padley 2011). About 10.4% of all UK infants who died in one UK-based study population had a cardiovascular malformation (Wren 2012). Adult re-operations are associated with significant morbidity and mortality with early mortality rates between 3.6% and 7.6%, and 15% to 24% of patients experiencing serious postoperative complications (Berdat 2004; Giamberti 2009). Research now focuses on further reducing mortality and maybe even more importantly, on decreasing perioperative morbidity (Gatzoulis 2005).

## Description of the intervention

Patients undergoing cardiac surgery for congenital heart disease are potentially exposed to red cell transfusion at many points in the surgical pathway; to treat anaemia preoperatively, correct blood loss during surgery, haemodilution while on cardiopulmonary bypass (CPB), and ongoing blood loss or haemodilution in the intensive care unit (ICU) or the ward post surgery.

CPB replaces the work of the heart and lungs allowing the heart to be stopped during surgery, providing a still and bloodless field for the surgeon (Allman 2002). The blood is oxygenated, carbon dioxide is removed and then the blood is returned to the patient. The circuit provides a continuous circulation between the venous cannula draining blood from the patient and the aortic cannula returning blood to the patient. The circuit tubing is primed with fluid to prevent air passing from the circuit into the patient. This fluid is known as the bypass prime and it may have a number of components (Allman 2002). If it does not contain any red cells, it is known as a clear or bloodless prime. As the bypass prime mixes with the patient's own circulation, there is a risk of excessive haemodilution so red cells are added to prevent this. Red cells can be added into the prime volume before bypass or into the bypass pump once the patient is on bypass. A neonate

is likely to undergo 60% haemodilution on bypass (Eaton 2005), so is almost always likely to have donor red cells added to the CPB prime (Groom 2005). However, a number of centres have been investigating bloodless CPB prime to reduce exposure to red cell transfusion (Ging 2008; Golab 2009; Miyaji 2007; Olshove 2010).

Despite improvements in the risks associated with red cell transfusion, many still exist. These risks can result in increased morbidity and mortality, especially in the critically ill patient population (Hebert 1999; Vincent 2002). In previous years, the major concerns were with the transmission of infection, especially hepatitis C virus and human immunodeficiency virus (HIV) (Guzzetta 2011; Morley 2009). Through donor screening and donation testing, the infectious risks are now small in developed countries with the quoted risk of hepatitis C being one in 100 million, hepatitis B one in one million and HIV one in 6.25 million (SHOT 2011). However, some countries do not have the same rigorous testing systems and infection transmission remains a real risk. The 2007 World Health Organization (WHO) Blood Safety Survey showed that out of 162 countries, 41 were not able to screen for one or more transfusion-transmissible infections (HIV, hepatitis B and hepatitis C) (WHO Blood 2013).

As transfusion medicine practice has developed and improved, the focus of risks associated with red cell transfusion has shifted to non-infectious sequelae with the main current issues of adverse transfusion reactions, acute lung injury and the negative effects of immunomodulation (Raghavan 2005).

Adverse transfusion reactions are a real concern. Children under 18 years old receive 4.2% of all red cell transfusions while children under one year old receive 1.7% (Wallis 2006). However, children have a disproportionately higher number of adverse reactions when compared with adults: 37 in 100,000 for children under one year old, 18 in 100,000 transfusion for children under 18 years, while for adults it is 13 in 100,000 (Stainsby 2008).

Transfusion-related acute lung injury (TRALI): new acute lung injury occurring during or within six hours of a transfusion (Lavoie 2011) is estimated to have an incidence between 0.08% and 15% of patients receiving a transfusion (Benson 2010; Silliman 2003) with an adult mortality of 5% to 10% (Vlaar 2013). Although reported to be rare in children, it is probably under-reported as it can be difficult to diagnose (Harrison 2011).

The negative effects of immunomodulation and red cell storage are increased nosocomial infections and the development of autoimmune diseases or cancer (Raghavan 2005; Sanchez 2005). Critically ill patients have been shown to have a six-fold incidence of developing a nosocomial infection when transfused with red cells compared with those not transfused and this incidence is dose-related with each additional unit of blood increasing the risk by a factor of 1.5 (Taylor 2002).

The recognition of these risks associated with red cell transfusion has led to a more critical appraisal of the use of red cell transfusion. Although red blood cells are transfused more frequently than any

other blood component, their overall usage in the UK has been declining with a decrease of around 20% in the 10 years from 1999/2000 (SHOT 2011).

Literature in critically unwell patient groups suggests that avoiding red cell transfusions may reduce morbidity, which explains the trend to reduce such exposure. Adult critical care patients subjected to a restrictive transfusion policy were shown to have a similar 30-day mortality during hospitalisation when compared with those with a liberal transfusion policy (18.7% versus 23.3%) (Hebert 1999), with red cell transfusions suggested as an independent predictor of death with an odds ratio of 1.7 (Marik 2008).

Relatively few studies have examined the effects of red cell transfusion on critically ill children (Istaphanous 2011). Lacroix reported the results of a prospective randomised controlled trial (RCTs) comparing a restrictive versus liberal transfusion strategy in critically ill children showing a decrease in transfusion requirements in the restrictive group without increasing adverse outcomes. The study did caution the use of a restrictive strategy in children with cyanotic heart disease (Lacroix 2007).

Neonatal studies have also examined restrictive versus liberal transfusion strategies. One of the largest studies, the Premature Infants in Need of Transfusion (PINT) study, suggested that a liberal transfusion strategy in extremely low birth weight neonates resulted in more infants receiving transfusions but conferred little evidence or benefit (Kirpalani 2006). When this study was combined with three others (Bell 2005; Chen 2009; Connelly 1998), a Cochrane review concluded that restrictive as compared with liberal transfusion thresholds resulted in modest reductions in transfusion and haemoglobin levels. Restrictive practice did not appear to have significant impact on death or major morbidities at hospital discharge or first hospital follow-up. However, there were uncertainties with these conclusions and further trials are needed (Whyte 2011).

## How the intervention might work

The most important physiological consequence of anaemia is reduced oxygen-carrying capacity of the blood. The optimal concentration of haemoglobin for avoidance of severe morbidity is unknown but animal experiments suggest the critical haemoglobin level for oxygen delivery to be 3 to 4 g/dL (Van der Linden 1998). Although healthy adult volunteers tolerate a haemoglobin of 5 g/dL with no increase in lactate production or decrease in oxygen consumption, they do show an increase in heart rate and a decline in cognitive function suggesting borderline tissue oxygen delivery (Weiskopf 2002). The physiological response to anaemia is to increase cardiac output so anaemia effectively consumes some of the cardiac reserve (Morley 2009). Patients with congenital heart disease and a marginal cardiac reserve often have a precarious oxygen supply/demand balance so anaemia may adversely alter this balance. Red cell transfusion augments tissue oxygen delivery by increasing the oxygen-carrying capacity of the blood (Guzzetta

2011). Many centres transfuse at a higher starting haemoglobin for patients with congenital heart disease when they require surgery or intensive care (Morley 2009).

The red cells that are transfused can vary in age and nature. They may or may not contain leukocytes, they may be fresh or old and they may come as packed cells or in whole blood. Each of these factors may be important in determining outcome for the transfusion recipient.

The negative immunomodulatory effects of red cell transfusion may be due to the presence of donor lymphocytes in transfused components (Morley 2009), and leukoreduction may reduce these negative effects (van de Watering 1998; van Hilten 2004).

Red blood cell function may become impaired with increased storage time (Morley 2009). Prolonged storage time may increase mortality, pneumonia, infection, multiorgan failure and length of hospital stay but these observations are based on laboratory and observational clinical studies and further work is needed (Tinmouth 2006).

Theoretically, whole blood should improve haemostasis and decrease systemic inflammation in comparison with packed red cells. Manno 1991 compared the immediate postoperative transfusion needs of children undergoing open-heart surgery with CPB with either whole blood or reconstituted whole blood (packed red cells, fresh frozen plasma and platelets). Transfusion with reconstituted blood significantly increased mean 24-hour postoperative blood loss in those less than two years old (85% more blood loss) but for those aged over two years undergoing surgery for simple defects, there was no significant difference between treatment groups. When whole blood was added into the bypass circuit prime, there were no significant differences in terms of bleeding and inflammatory mediator levels. There was a trend to longer ICU stay, greater positive fluid balance and longer hospital stay (Mou 2004).

In summary, the issues concerning red cell transfusion for patients with congenital heart disease relate to:

1. What haemoglobin trigger should blood be transfused - can patients tolerate a lower (restrictive) haemoglobin concentration before they need to be transfused?
2. How much blood to give - what volume of red cell transfusion should be given to reach the intended haemoglobin target?
3. Leukoreduced versus non-leukoreduced - is there a benefit to removing leukocytes from the transfused red blood cells?
4. Whole blood versus packed cells - do patients benefit from whole blood more than packed red cells?
5. The age of red cells transfused: new versus old - do patients have better outcomes if they are transfused 'newer' red blood cells?

## Why it is important to do this review



The patient population with congenital heart disease is small but they are surviving longer. Epidemiological studies have confirmed this decreasing mortality and prolonged survival in young patients resulting in a growing and ageing population with congenital heart disease (Khairy 2010; Knowles 2012; Wren 2001).

Although mortality and morbidity have improved, cardiac surgery for congenital heart disease remains a risk especially in neonatal, premature and those undergoing complex surgery populations. Blood transfusion has been associated with adverse outcomes in other critically unwell patient populations and the specialty of congenital heart disease has begun to address the specific risks to this population (Guzzetta 2011). Studies have tried to elicit the risk factors for adverse outcomes in patients undergoing surgery for congenital heart disease (Székely 2006). One secondary analysis suggested that intraoperative and early postoperative blood transfusion was a powerful independent predictor of duration of mechanical ventilation in infants undergoing reparative cardiac surgery (Kipps 2011). Infants receiving the highest volume of transfusion had a hazard of remaining intubated that was twice as high as infants receiving the lowest volume of transfusion. The total amount of blood transfusion has been independently associated with infections but not mortality (Székely 2009). Red cell transfusions have also been associated with longer hospital stay with the strongest association in the high transfusion group (Salvin 2011). This association was limited to patients with a biventricular and not a univentricular circulation. For patients with hypoplastic left heart syndrome, a higher haemoglobin nadir on postoperative days two to five was associated with higher early mortality but neither haemoglobin concentrations nor transfusions were associated with two-year mortality or neurodevelopmental outcomes. More transfusions two to five days postoperatively were associated with morbidity measured by ventilation days (Blackwood 2010).

There are no systematic reviews examining red cell transfusion in this patient population (Dorée 2010). Unanswered clinical questions include at what haemoglobin concentration should blood be given, how much blood should be given, what age (new versus old) and what type of blood should be used (leukoreduced or non-leukoreduced, irradiated or non-irradiated, packed cells or whole blood). This review aims to address these knowledge gaps and direct future research and clinical practice.

Although the three patient groups of neonates, paediatrics and adults appear different, the same questions exist for all of them and it is likely that a neonate will survive to adulthood and possibly require further surgery at a later stage. We assessed the three groups separately but kept them in the same review. Clinicians often manage these patients from birth to adulthood so the review will cover all ages.

## OBJECTIVES

To evaluate the effects of red cell transfusion on mortality and morbidity on patients with congenital heart disease at the time of cardiac surgery.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included RCTs in this review.

#### Types of participants

We included all patients undergoing cardiac surgery for congenital heart disease with no restriction on age. The congenital heart disease could be cyanotic or acyanotic. We grouped patients by age: neonates (newborns up to four weeks old), paediatrics (children four weeks post birth to age 16 years) and adults (over 16 years) and analysed them separately.

We excluded patients with congenital heart disease undergoing non-cardiac surgery and considered all co-morbidities.

#### Types of interventions

The intervention was red cell transfusion at any point in the surgical pathway. This included red cell transfusion intraoperatively directly into the patient or into the CPB machine (either into the prime cardiopulmonary volume before bypass or subsequently into the cardiopulmonary pump volume during bypass) or post-operatively during their hospital stay.

We included the following comparisons:

- Restrictive transfusion trigger versus liberal transfusion trigger – blood was transfused at two or more different patient haemoglobin concentrations with liberal transfusion trigger being higher than restrictive (different studies chose different haemoglobin concentrations but were around haemoglobin 7 to 8 g/dL for restrictive and 9 to 10 g/dL for liberal).
- Volume A red cell transfusion versus volume B red cell transfusion (e.g. higher volume versus lower volume (different mL/kg)). The standard advised resuscitation volume for paediatric patients is 20 mL/kg so the doses were likely to be factors of 20 mL/kg.
- Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion.
- Whole blood versus packed red cell transfusion.
- 'New' (not near to expiry date) versus 'old' (near to expiry date) red cell transfusion. In the UK, red blood cells up to five days old may be given for neonates and up to 35 days old for

paediatric patients so each group contained comparison groups appropriate to the suggested national guidelines (BCSH 2004).

- Standard CPB prime versus non-standard CPB prime (e.g. bloodless prime or different methods of processing the prime).

## Types of outcome measures

### Primary outcomes

- All-cause mortality: short term (0 to 30 days post surgery).

### Secondary outcomes

- All-cause mortality: long term: 30 days to two years post surgery.
- Severe adverse events: cardiac events, acute lung injury, stroke, thromboembolism, renal failure (needing renal replacement therapy), infection, haemorrhage (return to theatre for bleeding).
- Haematocrit/haemoglobin (g/dL) concentrations post operative and at discharge.
- Volume or number of red cell units transfused.
- Volume or number of other blood products transfused (i.e. fresh frozen plasma, platelets, cryoprecipitate).
- Postoperative chest drain output.
- Duration of mechanical ventilation.
- Duration of ICU stay.
- Re-hospitalisation rates.
- Biochemistry levels (added post-hoc).

## Search methods for identification of studies

### Electronic searches

The Systematic Review Initiative's information specialist (CD) formulated the search strategies in collaboration with the Cochrane Heart Group. We searched the following databases.

### Bibliographic databases

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 5, 2013).
- MEDLINE (Ovid) (1950 to 11 June 2013).
- EMBASE (Ovid) (1980 to 11 June 2013).
- PubMed (e-publications only: searched 11 June 2013).
- CINAHL (EBSCO) (1982 to 11 June 2013).
- LILACS (searched 11 June 2013).
- Transfusion Evidence Library ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com)) (searched 11 June 2013).

- Conference Proceedings Citation Index - Science (Web of Science) (1990 to 11 June 2013).
- IndMed (searched 11 June 2013).
- KoreaMed (searched 11 June 2013).
- PakMediNet (searched 11 June 2013).

### Online databases of ongoing trials

- ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)) (searched 11 June 2013).
- ISRCTN Register ([www.controlled-trials.com/isrctn/](http://www.controlled-trials.com/isrctn/)) (searched 11 June 2013).
- WHO International Clinical Trials Registry Search Platform (WHO ICTRP) ([apps.who.int/trialsearch/AdvSearch.aspx](http://apps.who.int/trialsearch/AdvSearch.aspx)) (searched 11 June 2013).

We modified the search strategy that was used to search MEDLINE to search the other databases listed. Searches in MEDLINE were combined with the Cochrane RCT search filter as detailed in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We combined searches in EMBASE and CINAHL with adaptations of the relevant Scottish Intercollegiate Guidelines Network (SIGN) RCT filters ([www.sign.ac.uk/methodology/filters.html](http://www.sign.ac.uk/methodology/filters.html)). The search strategies for all databases are available in Appendix 1. We applied no restrictions by language of publication or publication status.

### Searching other resources

We also:

- handsearched reference lists;
- checked references of all identified trials and relevant review articles for further literature. We limited these searches to the 'first generation' reference lists;
- handsearched conference proceedings;
- searched abstracts (published between 2006 and January 2011) of the most relevant conferences for further studies, including the European Society of Cardiology, World Congress of Cardiology, American Heart Association, Society of Cardiothoracic Surgeons, British Cardiovascular Society, European Association of Cardiothoracic Surgeons, American Association for Thoracic Surgery and Association for European Paediatric and Congenital Cardiology.

## Data collection and analysis

### Selection of studies

One review author (CD) screened all electronically derived citations and abstracts of papers identified by the review search strategy. We excluded studies that were clearly irrelevant (e.g. non-RCTs, non-cardiac surgery papers and duplicates) at this stage.

Two review authors (KW, SB) independently assessed the titles and abstracts of all potentially relevant trials for eligibility. We obtained the full text of any papers where eligibility could not be assessed on title and abstract alone and two review authors (KW, SB) independently assessed eligibility. At all stages, we resolved any disagreements by discussion or by consultation with a third review author (MM). We sought further information from the study authors where articles contained insufficient data to make a decision about eligibility. We designed a study eligibility form to help in the assessment of relevance using the criteria outlined above.

### Data extraction and management

Two review authors (KW, SB) independently conducted data extraction according to the guidelines proposed by The Cochrane Collaboration. We resolved disagreements by consensus. The review authors were not blinded to names of authors, institutions, journals or the outcomes of the trials. We extracted data from the studies using a standardised data extraction form. The form was initially piloted on a sample of the eligible papers and any disagreements were resolved before the rest of the data extraction was completed.

We used both full-text versions and abstracts including additional information (e.g. slides) of eligible studies to retrieve the data. We extracted trials reported in more than one publication on one form only. Where these sources did not provide sufficient information, we requested additional details from the contact author.

### Assessment of risk of bias in included studies

Two review authors (KW, SB) assessed all included studies for possible risk of bias, using the 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). The assessment included information about the design, conduct and analysis of the trial. We evaluated the criteria using a three-point scale: low, high or unclear risk of bias.

### Measures of treatment effect

For dichotomous outcomes, the numbers of outcomes in treatment and control groups were recorded and the risk ratio (RR) was reported with a 95% confidence interval (CI) that was used for reporting the treatment effect measures across individual studies. For continuous outcomes, the mean and standard deviations (SD) were recorded. For continuous outcomes measured using the same scale, the effect measure was the mean difference (MD) with 95% CIs, and, if data had necessitated, the standardised mean difference (SMD) for outcomes measured using different scales. Three trials reported standard error of the means (SEM) (Komai 1998; Liu 2007; Swindell 2007): we calculated SDs from the SEM and used these for our calculations throughout this review.

Five trials reported outcome data using median values (with interquartile ranges) (Cholette 2011; Cholette 2012; de Vries 2004; Shimp 2001; Ye 2013): these values have been commented on in the text and individual outcome data reported in Table 1; Table 2; Table 3; and Table 4. The trials report that some of their outcome data were reported as median and interquartile ranges due to a skew in particular distributions. Such skew is commonplace in measures of duration (e.g. duration of mechanical ventilation and length of hospital stay) and thus was expected by the authors of this review.

Two trials reported data that could have allowed a change from baseline analysis to be undertaken (Han 2004; Komai 1998). However, as no change from baseline SDs were reported by these trials, we have chosen to not calculate change from baseline scores. The findings from these studies has been reported using MDs with 95% CIs as per all other continuous outcomes in this review.

We had planned to calculate the number needed to treat for an additional beneficial outcome (NNTB) with 95% CI and the number needed to treat for an additional harmful outcome (NNTH) with 95% CI but were unable to do so as we had insufficient relevant data to undertake this calculation.

### Unit of analysis issues

We did not encounter any unit of analysis issues, as we did not include any cluster-randomised trials in this review, and the unit of analysis and randomisation was always the patient. If any unit of analysis issues had arisen, we would have treated these in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Dealing with missing data

We successfully contacted three study authors by email to obtain missing data. One was contacted for more information on randomisation sequence as it was unclear in the published report (Komai 1998). The second was contacted to request clarity on outcome data and information on whether study personnel were blinded to treatment allocation (Cholette 2012). The third was contacted to clarify some outcome data and in response we received the mean and SD values for the baseline characteristics and outcomes they reported in their manuscript (Ye 2013).

Where possible, we used intention-to-treat (ITT) data, but if not we included per-protocol (PP) data. One trial stated that they analysed data by both ITT and PP but the manuscript reported baseline data by ITT and outcome assessment data by PP (Cholette 2012). A second trial reported both ITT and PP data for their primary outcome: with the results being very similar by both analyses (Willems 2010). In accordance with our protocol, we have used the ITT data from this trial in our review.

## Assessment of heterogeneity

We did perform any meta-analyses in this review, thus we did not make a formal assessment of heterogeneity. Should there have been sufficient data to support meta-analyses, the decision about whether or not to combine the results of individual studies would have depended on an assessment of heterogeneity. We would have assessed statistical heterogeneity of treatment effects between trials using a  $\text{Chi}^2$  test with a significance level at  $P$  value  $< 0.1$ . We would have used the  $I^2$  statistic to quantify the percentage of heterogeneity ( $I^2 > 30\%$  moderate heterogeneity,  $I^2 > 75\%$  considerable heterogeneity). We would have explored potential causes of heterogeneity using sensitivity and subgroup analyses. In any future updates of this review, assuming we find sufficient data, we will perform assessment of heterogeneity as outlined.

## Assessment of reporting biases

As there were no meta-analyses with more than 10 trials, we did not perform an assessment of reporting biases. In future updates of this review, we will explore potential publication bias (small trial bias) by generating a funnel plot and do statistical testing using a linear regression test. A  $P$  value of less than 0.1 would be considered significant for this test (Lau 2006; Sterne 2011).

## Data synthesis

We performed analyses according to the recommendations of The Cochrane Collaboration (Schunemann 2011), with aggregated data used for analysis. For statistical analysis, we used Review Manager 5 (RevMan 2012).

We used a fixed-effect model for meta-analysis and employed the Mantel-Haenszel method for dichotomous data outcomes (and the generic inverse variance method for survival data outcomes, should this data have been available). We found no unexplained statistical heterogeneity, but if we had, we would have undertaken a random-effects meta-analysis, and reported both fixed-effect and random-effects meta-analyses. As most outcome data did not allow for meta-analysis (due to clinical and outcome diversity), we have reported outcome data descriptively.

We created no 'Summary of findings' table for this review due to the lack of reported data across the included trials. If we had been able to produce a 'Summary of findings' table, we would have used the GRADE profiler as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2011a).

## Subgroup analysis and investigation of heterogeneity

Sufficient data were not available to perform our intended subgroup analyses relating to whether a patient had acyanotic or cyanotic congenital heart disease and the timing of the transfusion: preoperatively, intraoperatively, postoperatively. In future updates of this review, we will explore these subgroup analyses should we find appropriate data.

## Sensitivity analysis

We had intended to assess the robustness of our findings by the following sensitivity analyses:

- including only those trials at low risk of bias on the dimensions of selection and performance bias (clinicians only);
- including only those trials in which 25% of patients or less were lost to follow-up.

However, there were insufficient data to enable these assessments. In future updates of this review, we will explore these sensitivity analyses should we find appropriate data.

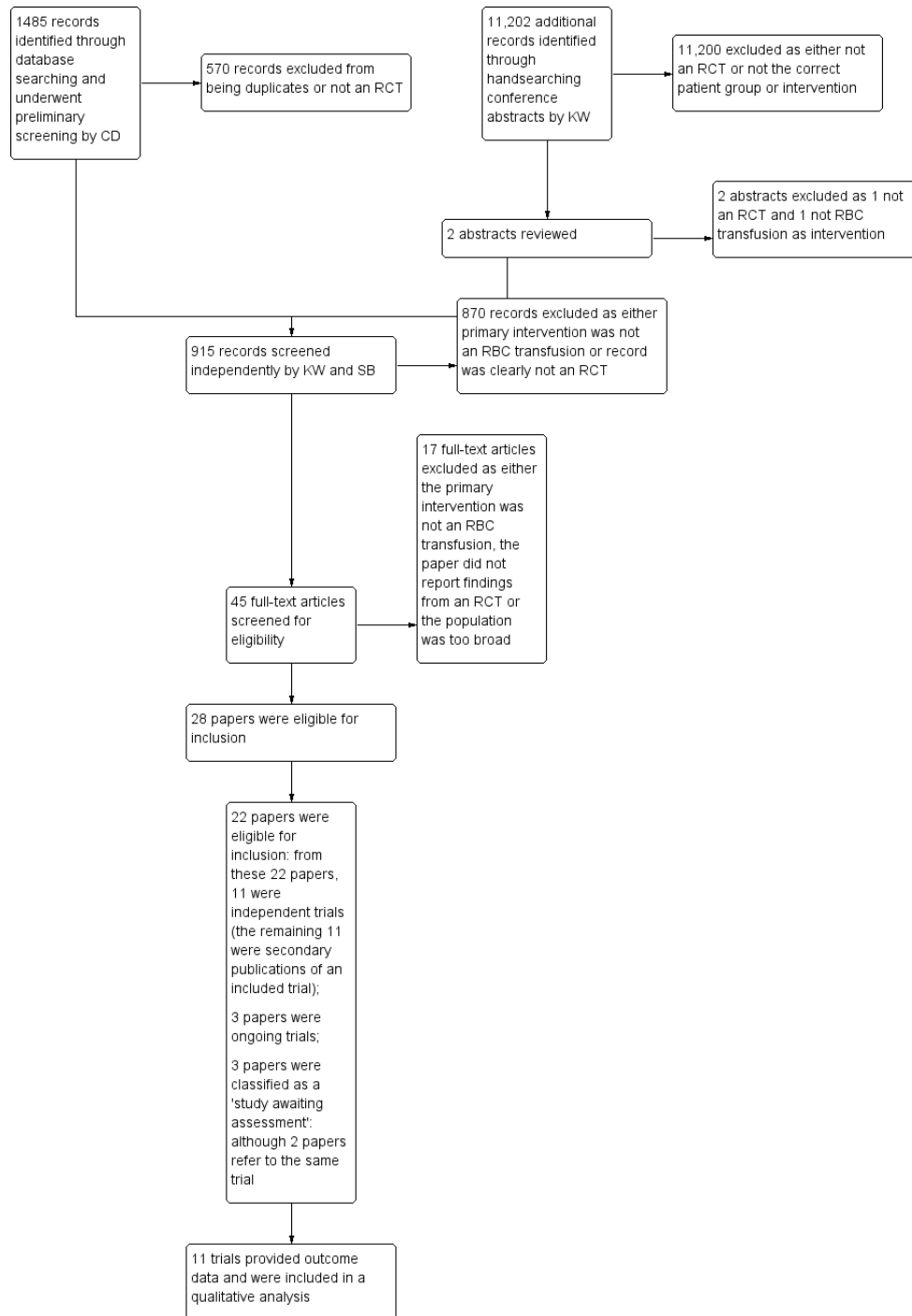
# RESULTS

## Description of studies

### Results of the search

The database search identified 1485 references. After initial screening of the database citations, we excluded 570 for being duplicates or not an RCT. We screened the remaining 915 records according to the criteria defined above and excluded 870 (see Figure 1).

**Figure 1. Study flow diagram.**



Handsearching of the abstracts from the annual conference proceedings identified 11,202 references. After initial screening, we excluded all but two as they were either not the correct intervention or not an RCT. We excluded the two remaining abstracts after obtaining further information: one was not an RCT and the other did not solely use red blood cells as the intervention.

We obtained the full text of 45 references. We deemed 23 references (providing data on 11 independent trials) eligible for inclusion, identified three references (providing data on two separate trials) as a 'trial awaiting assessment', found three references to be ongoing trials and excluded 17 references for not meeting the eligibility criteria of this review.

### Included studies

We found 11 trials (from 22 references) to be eligible for inclusion in this review (see [Characteristics of included studies](#) table).

### Design

The trials were published between 1990 and 2013 and all were published in English as full journal articles. All trials were parallel RCTs. One paper ([Willems 2010](#)) was a sub-study analysis of a larger RCT ([Lacroix 2007](#)). The larger trial was not eligible for inclusion in our review as it examined the general paediatric intensive care population and was not specific to children with congenital heart disease undergoing cardiac surgery ([Lacroix 2007](#)). The sub-study of [Willems 2010](#) explored transfusion strategies for paediatric patients undergoing surgery for congenital heart disease in paediatric intensive care units (PICU).

### Sample sizes

The trials included 862 patients. The number of patients ranged from 16 ([Liu 2007](#)) to 309 ([Ye 2013](#)). Three trials reported inadequate powering of their studies with reference to testing for statistical differences in clinical outcomes ([Cholette 2011](#); [Cholette 2012](#); [Willems 2010](#)).

### Setting

The trials were conducted in eight countries with three trials in the US ([Cholette 2012](#); [Cholette 2011](#); [Hosking 1990](#)); two in China ([Liu 2007](#); [Ye 2013](#)); and one in each of Japan ([Komai 1998](#)), Germany ([Shimpo 2001](#)), the Netherlands ([de Vries 2004](#)), Korea ([Han 2004](#)), and UK ([Swindell 2007](#)). One trial was multi-country, with patients included from Belgium, Canada and the US ([Willems 2010](#)).

### Patients

The patients were neonates or children. There were no trials including adults with congenital heart disease. One trial looked at neonates only ([Liu 2007](#)), two trials included both neonates and children ([Cholette 2012](#); [Swindell 2007](#)). The remaining eight trials examined children only ([Cholette 2011](#); [de Vries 2004](#); [Han 2004](#); [Hosking 1990](#); [Komai 1998](#); [Shimpo 2001](#); [Willems 2010](#); [Ye 2013](#)). Three trials included only cyanotic patients ([Cholette 2011](#); [Liu 2007](#); [Swindell 2007](#)), four trials only acyanotic patients ([Han 2004](#); [Komai 1998](#); [Shimpo 2001](#); [Willems 2010](#)), and four trials included both cyanotic and acyanotic patients ([Cholette 2012](#); [de Vries 2004](#); [Hosking 1990](#); [Ye 2013](#)).

### Interventions

The trials examined red cell transfusion as an intervention in several different ways (see [Table 5](#)).

Two trials assessed a restrictive versus a liberal red blood cell transfusion policy ([Cholette 2011](#); [Willems 2010](#)). In the restrictive arm, children (with single ventricle physiology post cavopulmonary connection (cyanotic group)) were transfused when their haemoglobin concentration was less than 9.0 g/dL ([Cholette 2011](#)), or when their haemoglobin concentration was less than 7.0 g/dL ([Willems 2010](#)). In the liberal arm, children (with new or progressive multiple organ dysfunction post cardiac surgery (acyanotic group) received a red blood cell transfusion when their haemoglobin concentration was greater than 13.0 g/dL ([Cholette 2011](#)), or when their haemoglobin concentration was less than 9.5 g/dL ([Willems 2010](#)).

Two trials assessed the impact of leukoreduction but at different time points in the operation and in different patient populations. One trial, in acyanotic neonates and paediatric patients, explored the benefits (postoperative oxygenation and circulating leukocyte counts) of a leukoreduction filter for the blood in the bypass circuit at the end of the operation ([de Vries 2004](#)). The other trial, in acyanotic paediatric patients, reported on the clinical effect (lung function) of applying leukoreduction filters to stored donor red blood cells added to the CPB circuit at the beginning of the operation ([Komai 1998](#)).

Seven trials assessed red blood cell usage during CPB, but each was for a different aspect of non-standard CPB prime. In addition, the age of the patients and inclusion of acyanotic or cyanotic patients differed between the trials. Three of these trials assessed the impact of washing packed red blood cells ([Cholette 2012](#); [Hosking 1990](#); [Swindell 2007](#)): in two trials the red blood cells had also been irradiated ([Cholette 2012](#); [Swindell 2007](#)); one trial assessed CPB prime containing red blood cells versus crystalloid (bloodless) prime ([Han 2004](#)); one trial assessed cell salvage versus no cell salvage during CPB ([Ye 2013](#)); one trial compared the effects of

unprocessed and processed packed red cells with the continuous autologous transfusion system (Liu 2007); and one trial compared red blood cells that had been ultrafiltrated versus red blood cells that had not been ultrafiltrated (Shimpo 2001).

## Outcomes

No trial measured all outcomes of interest to this review. Two trials did not include any outcomes pre-defined as of interest to this review (Hosking 1990; Swindell 2007). However, they both included an outcome (biochemistry levels) that should be relevant to this review (and may be important in any future updates). We have added this outcome into this review, clearly marking it as an outcome that was identified and added after the review protocol was agreed.

## Excluded studies

We excluded 17 studies from the review following full-text eligibility assessment (see Characteristics of excluded studies table). In summary, eight studies were not RCTs; seven had an incorrect intervention (five did not analyse red blood cell independently of other blood products) and two had an incorrect patient popula-

tion (one contained neonates with cardiac neonates but they did not undergo cardiac surgery and one was in the general neonatal population).

## Studies awaiting classification

We included two trials (from three references) in the 'studies awaiting classification' section of the review (see Characteristics of studies awaiting classification table).

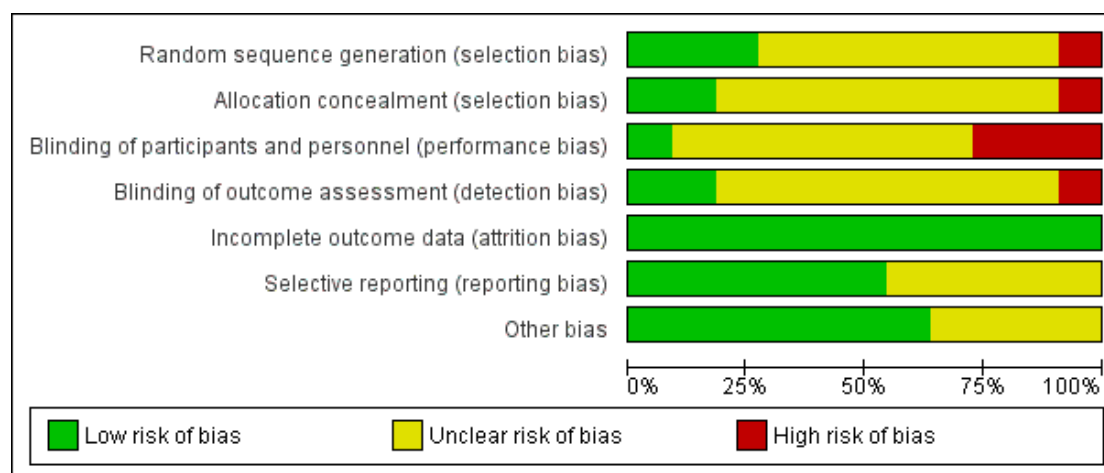
## Ongoing studies

We identified three ongoing studies (see Characteristics of ongoing studies table). We will monitor the progress of these trials and, on publication (assuming eligibility), will include them in future updates of this review. The ongoing RCTs cover two interventions: transfusion triggers (Cholette 2012a; Reeves 2008), and age of red blood cells to be transfused (Steiner 2010).

## Risk of bias in included studies

See the 'Risk of bias' tables for details of our assessment for each study and Figure 2 and Figure 3 for a 'Risk of bias' graph and tabular summary.

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





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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cholette 2011	?	?	-	?	+	+	+
Cholette 2012	?	?	-	-	+	+	+
de Vries 2004	+	-	?	?	+	+	+
Han 2004	+	?	?	?	+	?	?
Hosking 1990	?	?	?	?	+	?	?
Komai 1998	-	?	?	?	+	?	+
Liu 2007	?	?	?	?	+	+	+
Shimpo 2001	?	+	+	+	+	?	?
Swindell 2007	?	?	?	?	+	+	+
Willems 2010	+	+	-	+	+	+	+
Ye 2013	?	?	?	?	+	?	?



## Allocation

Four trials reported details of the randomisation sequence (de Vries 2004; Han 2004; Komai 1998; Willems 2010). Three of these four trials were defined as being of low risk of bias, using computer generated lists (de Vries 2004; Han 2004) and assigning patients to intervention groups in blocks of two or four (Willems 2010). One trial was defined as being of high risk of bias as an alternation method was used (Komai 1998).

The generation of the randomisation sequence was defined as unclear risk of bias in the other seven trials (Cholette 2011; Cholette 2012; Hosking 1990; Liu 2007; Shimpo 2001; Swindell 2007; Ye 2013). Two trials used block randomisation to randomise into either transfusion strategy but no further description was provided as to how the random sequence was generated (Cholette 2011; Cholette 2012). Five trials did not report details of their generation of the randomisation sequence methods (Hosking 1990; Liu 2007; Shimpo 2001; Swindell 2007; Ye 2013), so we defined them as having an unclear risk of bias.

## Concealment of treatment allocation

The method of randomisation (as described above) was deemed to be of low risk of bias to conceal treatment allocation in two trials (Shimpo 2001; Willems 2010), where only the perfusionist was informed of allocation in one trial (Shimpo 2001), and the physicians, nurses and research staff were unaware of the block-randomisation strategy in the other trial (Willems 2010). One trial had its method of randomisation deemed inadequate (high risk of bias) to conceal treatment allocation, as the author confirmed directly by email that unsealed envelopes were used (de Vries 2004). Eight trials did not provide information to enable assessment of adequate allocation concealment (Cholette 2012; Cholette 2011; Han 2004; Hosking 1990; Komai 1998; Liu 2007; Swindell 2007; Ye 2013); therefore, we defined them as having unclear risk of bias.

## Blinding

Blinding of patients, clinicians or outcome assessors was reported in four trials (Cholette 2012; Cholette 2011; Shimpo 2001; Willems 2010). In one trial, only the perfusionist was informed of trial allocation and all other people involved in the trial were blind to treatment allocation (low risk of bias) (Shimpo 2001). We defined blinding as high risk of bias in the other three trials: no-one involved in the care of or outcome assessment of the patients was blinded to treatment allocation (Cholette 2012); the blinding of personnel and patients was inadequate as clinical staff and patients' families were aware of transfusion group assignment while the blinding of the outcome assessors was not reported so rated as unclear risk of bias in the one trial (Cholette 2011). In the third

trial (Willems 2010), blinding of personnel and patients was also of high risk of bias, but the outcome assessors were stated as being "unaware of treatment assignment" and we have defined blinding as at a low risk of bias for outcome assessors.

The blinding of all trial personnel (patients, clinicians and outcome assessors) to treatment allocation was unclear in seven trials (de Vries 2004; Han 2004; Hosking 1990; Komai 1998; Liu 2007; Swindell 2007; Ye 2013).

## Incomplete outcome data

Eight trials included all randomised patients in the analysis of outcome data and did not lose any patients during follow-up (de Vries 2004; Hosking 1990; Komai 1998; Liu 2007; Shimpo 2001; Swindell 2007; Willems 2010; Ye 2013). The remaining three trials did not include all randomised patients in the analysis of clinical, scientific or both clinical and scientific outcomes, but reported reasons for this non-inclusion (Cholette 2011; Cholette 2012; Han 2004).

In Cholette 2012, no patient was lost to follow-up, but six patients were excluded following randomisation for reported surgical reasons. Following randomisation, a further 34 patients (17 in each treatment arm) did not receive a transfusion and, therefore, were not included in the PP analysis. In Cholette 2011, two randomised patients (3% of patients in this trial) were excluded from the trials and, therefore, outcome analysis (one patient from each intervention arm). No other patient dropped out of the study or was lost to follow-up. In Han 2004, one patient (3% of patients in this trial) in the intervention group was excluded for clinical reasons and this patient's data were not included in any outcome analyses.

## Selective reporting

In six RCTs, all outcomes defined in their methods section were reported on in their results section (low risk of bias) (Cholette 2012; Cholette 2011; de Vries 2004; Liu 2007; Swindell 2007; Willems 2010). Four RCTs did not define the outcomes they were interested in; therefore, it is impossible to identify whether there was reporting bias in these trials (Han 2004; Hosking 1990; Komai 1998; Shimpo 2001; Ye 2013), and we have rated them as having unclear risk of bias.

## Other potential sources of bias

### Protocol adherence

Three trials reported protocol adherence (Cholette 2011; Cholette 2012; Willems 2010). In one trial, there was 100% compliance

with the trial protocol and the protocol was never suspended during the trial (Chollette 2011). There were three protocol violations in one trial; one in a neonate receiving washed red blood cells and two in neonates in the unwashed red blood cell group (Chollette 2012). In the other trial, 10 patients did not reach their pre-defined criteria for good protocol adherence (80%) and seven patients in the restrictive group and one in the liberal group were suspended temporarily from the transfusion protocol (Willems 2010).

### Support and sponsorship

Eight trials did not report the source of funding (de Vries 2004; Han 2004; Hosking 1990; Komai 1998; Liu 2007; Shimp 2001; Swindell 2007; Ye 2013). In the three trials that reported source of funding, two trials were supported in part by university grants (Chollette 2011; Chollette 2012) and the study authors did not disclose any potential conflicts of interest. The third trial was supported by government grants from the Canadian Institutes of Health Research (CIHR) and Fonds de la Recherche en Sante du Quebec (FRSQ). The authors conflicts of interest were reported and we assessed them as low risk of bias (Willems 2010).

### Effects of interventions

The outcome data in this review are reported by outcome and then by intervention. Relevant eligible trials were only identified for three of the interventions of interest: restrictive transfusion trigger versus liberal transfusion trigger; leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion; and standard CPB prime versus non-standard CPB prime.

The clinical diversity in the patient groups (cyanotic and acyanotic, and paediatric and neonate) has meant that there was no opportunity to pool data within these intervention groups. In addition, no data was pooled across the intervention standard versus non-standard CPB prime due to clinical diversity in the patient groups and also due to differences in the red blood cells (processed versus unprocessed, washed versus unwashed) used in the CPB machine.

### Primary outcome

#### All-cause mortality: short term (30 days post surgery)

##### Restrictive transfusion trigger versus liberal transfusion trigger

Willems 2010 reported data for this outcome. There was no difference in the number of deaths between the restrictive and liberal threshold (RR 0.98, 95% CI 0.14 to 6.77, 125 patients). The time at which death occurred and the causes of death were not reported (Figure 4).

##### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

##### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Four trials report measuring this outcome (Chollette 2012; Liu 2007; Shimp 2001; Ye 2013), although incidents of mortality were only reported in two trials (Chollette 2012; Ye 2013), as Liu 2007 and Shimp 2001 reported no in-hospital deaths in their trials. We did not perform a meta-analysis due to clinical and intervention diversity.

There were no differences in the number of deaths between the intervention arms (RR, 95% CI 0.03 to 2.18; 128 patients, Chollette 2012; RR 0.21, 95% CI 0.02 to 2.31, 309 patients, Ye 2013) (Figure 4). Where reported, details of the cause and time of death are provided in Table 6.

### Secondary outcomes

#### All-cause mortality: long term (at two years)

##### Restrictive transfusion trigger versus liberal transfusion trigger

Chollette 2011 reported data for this outcome. There was no difference in the number of deaths over a long (up to two years post surgery) period between the restrictive and liberal threshold group (RR 0.33, 95% CI 0.01 to 7.87, 60 patients) (Analysis 1.2).

##### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

##### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Data for this outcome were obtained directly from the study author for one trial (Chollette 2012). There was no difference in the number of deaths over a long time period (at two years) between the washed intervention and the unwashed intervention groups (RR 0.33, 95% CI 0.07 to 1.59, 128 patients) (Analysis 1.2). Details of the cause and time of death are provided in Table 6.

### Severe adverse events: cardiac events

#### Restrictive transfusion trigger versus liberal transfusion trigger

Willems 2010 reported data for this outcome. There was no difference in the number of patients who had cardiovascular dysfunction between the restrictive and liberal trigger arms (RR 0.98, 95% CI 0.71 to 1.36, 125 patients) (Analysis 1.3). No further details were given as to when the dysfunction occurred, how it was treated or the outcome for these patients.

#### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

#### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Cholette 2012 reported data for this outcome, defining a cardiac event as arrhythmia that was haemodynamically significant, required intervention or both. There was no difference in the number of patients who had a cardiac event at any time during the hospital admission between the intervention arms (RR 0.88, 95% CI 0.47 to 1.64, 128 patients) (Analysis 1.3).

### Severe adverse events: acute lung injury

#### Restrictive transfusion trigger versus liberal transfusion trigger

Willems 2010 reported data for this outcome. There was no difference in the number of patients experiencing an acute lung injury between intervention arms (RR 0.96, 95% CI 0.73 to 1.26, 125 patients) (Analysis 1.4). No further details were given as to when the acute lung injury occurred, how it was treated or the outcome for these patients.

#### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

#### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Ye 2013 reported data for this outcome. There was no difference in the number of patients experiencing an acute lung injury between the cell salvage and the no-cell salvage treated groups (RR 0.88, 95% CI 0.61 to 1.27, 309 patients) (Analysis 1.4). No further

details were given as to when the acute lung injury occurred, how it was treated or the outcome for these patients.

### Severe adverse events: stroke

No trial reported data for this outcome.

### Severe adverse events: thromboembolism

#### Restrictive transfusion trigger versus liberal transfusion trigger

No trial reported data for this outcome.

#### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

#### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Cholette 2012 reported data for this outcome. There was no difference in the number of patients who had a thromboembolism, at any time during the hospital admission, between the washed intervention and unwashed intervention groups (RR 0.88, 95% CI 0.34 to 2.27, 128 patients) (Analysis 1.5).

### Severe adverse events: renal failure (needing renal replacement therapy)

#### Restrictive transfusion trigger versus liberal transfusion trigger

Willems 2010 reported data for this outcome. There was no difference in the number of patients experiencing renal failure between the intervention arms (RR 0.33, 95% CI 0.01 to 7.90, 125 patients) (Analysis 1.6). No details as to timing and severity of dysfunction were provided.

#### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

### **Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime**

[Ye 2013](#) reported data for this outcome. There was a difference in the number of patients experiencing renal failure, with patients receiving cell salvaged red blood cells during CPB being less likely to have renal failure than patients not exposed to cell salvage (RR 0.26, 95% CI 0.09 to 0.79, 309 patients) ([Analysis 1.6](#)).

### **Severe adverse events: infection**

#### **Restrictive transfusion trigger versus liberal transfusion trigger**

[Willems 2010](#) reported data for this outcome. There was no difference in the number of patients who had systemic inflammatory response syndrome between the intervention arms (RR 0.71, 95% CI 0.38 to 1.32, 125 patients) ([Analysis 1.7](#)).

#### **Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion**

No trial reported data for this outcome.

### **Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime**

[Cholette 2012](#) reported data for this outcome. There was no difference in the number of patients who had an infection at some time during their hospital admission between the washed and unwashed red blood cell intervention arms (RR 1.00, 95% CI 0.50 to 1.99, 128 patients) ([Analysis 1.7](#)). In all cases, a diagnosis of an infection was supported by culture data.

### **Severe adverse events: haemorrhage (return to theatre for bleeding)**

#### **Restrictive transfusion trigger versus liberal transfusion trigger**

[Cholette 2011](#) and [Willems 2010](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity. Neither trial reported a difference in the number of patients experiencing a haemorrhage requiring a return to theatre for bleeding between their intervention arms (RR 0.33, 95% CI 0.01 to 8.03, 60 patients, [Cholette 2011](#); RR 2.95, 95% CI 0.12 to 71.13, 125 patients, [Willems 2010](#)) ([Analysis 1.8](#)).

#### **Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion**

No trial reported data for this outcome.

### **Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime**

[Cholette 2012](#) reported data for this outcome. There was no difference in the number of patients experiencing a haemorrhage requiring a return to theatre for bleeding between the washed and unwashed red blood cell intervention groups (RR 0.33, 95% CI 0.01 to 8.03, 128 patients) ([Analysis 1.8](#)).

### **Haematocrit/haemoglobin (g/dL) levels postoperatively**

#### **Restrictive transfusion trigger versus liberal transfusion trigger**

[Cholette 2011](#) and [Willems 2010](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical and timing of outcome measurement diversity. There was a difference in haemoglobin concentrations after the first postoperative transfusion between the intervention arms favouring the restrictive threshold group in one trial (MD -1.20 g/dL, 95% CI -1.61 to -0.79, 125 patients, [Willems 2010](#)). The second trial found no difference in haemoglobin concentrations between the intervention arms when measured postoperatively (MD 0.10 g/dL, 95% CI -4.01 to 4.21, [Cholette 2011](#)) ([Analysis 1.9](#)).

#### **Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion**

No trial reported data for this outcome.

### **Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime**

[Han 2004](#), [Liu 2007](#), and [Ye 2013](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity. In all three trials, there was a difference in haematocrit levels postoperatively between the intervention arms. In [Han 2004](#), the difference favoured the CPB prime containing red blood cells (MD -3.90%, 95% CI -4.35 to -3.45, 36 patients); in [Liu 2007](#), the difference favoured the processed red blood cell group (MD 23.30%, 95% CI 6.01 to 40.59, 16 patients). In [Ye 2013](#), the difference favoured the cell salvage group (MD 1.19%, 95% CI 0.03 to 2.35, 309 patients) ([Analysis 1.9](#)).

### **Haematocrit/haemoglobin (g/dL) levels at discharge**

No trial reported data for this outcome.

## Volume or number of red blood cell units transfused

### Restrictive transfusion trigger versus liberal transfusion trigger

[Chollette 2011](#) and [Willems 2010](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity and how the outcome was measured. In one trial, there was a difference in the mean number of red blood cell units transfused within 48 hours of paediatric cardiac intensive care unit (PCICU) admission, favouring the restrictive threshold group (MD -1.67 units, 95% CI -2.15 to -1.19, 60 patients, [Chollette 2011](#)).

[Willems 2010](#) reported no difference in the volume of red blood cell units transfused between intervention arms (MD -1.00 mL/kg, 95% CI -2.35 to 0.35, 125 patients) ([Analysis 1.10](#)). [Willems 2010](#) also reported the total number of transfusions (13 in the restrictive red blood cell trigger group and 82 in the liberal group).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

[Komai 1998](#) reported data for this outcome. There was no difference in the mean number of red blood cell units transfused across the study period between the intervention arms (MD 0.30 units, 95% CI -0.32 to 0.92, 46 patients) ([Analysis 1.10](#)).

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

[Chollette 2012](#) reported data for this outcome. There was no difference in the mean number of red blood cell units transfused over the entire hospitalisation period between the washed and unwashed red blood cell intervention groups (MD -0.30 units, 95% CI -1.62 to 1.02, 128 patients) ([Analysis 1.10](#)).

## Volume or number of other blood products transfused (i.e. fresh frozen plasma, platelets, cryoprecipitate)

### Restrictive transfusion trigger versus liberal transfusion trigger

[Chollette 2011](#) and [Willems 2010](#) reported the number of patients receiving fresh frozen plasma and [Willems 2010](#) reported the number of patients receiving platelets. We did not undertake a meta-analysis due to clinical diversity and the timing of the outcome measurement. There was no difference between intervention arms in the number of patients receiving fresh frozen plasma in the first 48 hours after admission (RR 3.00, 95% CI 0.13 to 70.83, 60 patients) ([Chollette 2011](#)); in the number of patients receiving fresh frozen plasma up to 28 days following randomisation (RR 1.97, 95% CI 0.37 to 10.36, 125 patients) ([Willems 2010](#)), or in

the number of patients receiving platelets up to 28 days following randomisation (RR 1.23, 95% CI 0.35 to 4.37, 125 patients) ([Willems 2010](#)) ([Analysis 1.11](#); [Analysis 1.12](#)).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

[Chollette 2012](#) reported data for this outcome. There was no difference in the mean number of platelets, fresh frozen plasma and cryoprecipitate units transfused over the entire hospitalisation period between the washed and unwashed red blood cell intervention groups (platelets: MD -0.30 units, 95% CI -0.67 to 0.07; fresh frozen plasma: MD -0.17 units, 95% CI -0.47 to 0.13; cryoprecipitate: MD -0.11 units, 95% CI -0.27 to 0.05; 128 patients) ([Analysis 1.13](#); [Analysis 1.14](#); [Analysis 1.15](#)).

## Postoperative chest drain output

### Restrictive transfusion trigger versus liberal transfusion trigger

[Chollette 2011](#) (with 60 patients) reported data for this outcome. There was no difference in the mean volume of postoperative mediastinal tube drainage between the intervention arms at postoperative day 0 (MD -0.20 mL/kg/hour, 95% CI -0.88 to 0.48, 60 patients), postoperative day 1 (MD -0.20 mL/kg/hour, 95% CI -1.19 to 0.79, 60 patients) and postoperative day 2 (MD -0.20 mL/kg/hour, 95% CI -1.87 to 1.47, 60 patients) ([Analysis 1.16](#)).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

[Chollette 2012](#) and [Ye 2013](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity and differences in how the outcome was measured. In both trials, there was no difference between the intervention arms in the mean duration of postoperative chest drain output (MD 0.14 days, 95% CI -1.66 to 1.94, 128 patients, [Chollette 2012](#)) or in the mean volume of postoperative chest drain output (MD -0.18 mL/kg, 95% CI -2.20 to 1.84, 309 patients, [Ye 2013](#)) ([Analysis 1.16](#)).



## Duration of mechanical ventilation

### Restrictive transfusion trigger versus liberal transfusion trigger

[Cholette 2011](#) and [Willems 2010](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity and the method of statistical analysis. [Cholette 2011](#) reported the length of mechanical ventilation as median (plus interquartile range). The restrictive threshold group requiring a greater duration of mechanical ventilation than the liberal threshold group. The skew of this data prevents a conversion to mean (and SD). Median values are reported in [Table 3](#). In the second trial ([Willems 2010](#)), there was no difference in the length of mechanical ventilation between the treatment arms after randomisation (MD -0.70 hours, 95% CI -2.01 to 0.61, 125 patients) and for total PICU stay (MD -0.10 hours, 95% CI -1.48 to 1.28, 125 patients) (see [Figure 5](#)).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

[de Vries 2004](#) and [Komai 1998](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity and the method of statistical analysis. [de Vries 2004](#) reported intubation time as median (plus interquartile range). The non-leukoreduced group required a greater duration of mechanical ventilation than the leukoreduced group. The skew of this data prevents a conversion to mean (and SD). Median values are reported in [Table 3](#). In the second trial ([Komai 1998](#)), there was no difference in intubation time between the two groups (MD -7.20 hours, 95% CI -20.62 to 6.22, 48 patients) ([Analysis 1.17](#)).

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

[Shimpo 2001](#), [Cholette 2012](#), and [Ye 2013](#) reported measuring this outcome. We did not undertake a meta-analysis due to lack of suitable data. Two trials reported intubation time as median (plus interquartile range) ([Cholette 2012](#); [Ye 2013](#)). In [Cholette 2012](#), the comparator group (unwashed red blood cells) required a greater duration of mechanical ventilation than the interventions group (washed red cell group), while in [Ye 2013](#), the intervention group (cell salvage) required a greater duration of mechanical ventilation than the control group. The skew of this data prevents a conversion to mean (and SD). Median values are reported in [Table 3](#). No data were reported by the third trial ([Shimpo 2001](#)).

## Duration of intensive care unit stay

### Restrictive transfusion trigger versus liberal transfusion trigger

[Cholette 2011](#) and [Willems 2010](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity. There was no difference in the length of hospital stay between the restrictive and liberal threshold in both trials (MD 1.20 days, 95% CI -1.38 to 3.78, 60 patients, [Cholette 2011](#); MD -0.40 days, 95% CI -2.42 to 1.62, 125 patients, [Willems 2010](#)) ([Figure 6](#)).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

[de Vries 2004](#) and [Komai 1998](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity. [de Vries 2004](#) reported similar lengths of median ICU stay for both groups. Median values are reported in [Table 4](#). In [Komai 1998](#), there was no difference in the duration of ICU stay between the two groups (MD -1.10 days, 95% CI -2.21 to 0.01, 46 patients) ([Figure 6](#)).

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

[Shimpo 2001](#) and [Cholette 2012](#) reported data for this outcome. We did not undertake a meta-analysis due to clinical diversity in the intervention arms. In [Shimpo 2001](#), there was a difference in the mean length of ICU stay favouring the ultrafiltration treated arm (MD -16.00 hours, 95% CI -21.89 to -10.11, 100 patients), but in [Cholette 2012](#), there was no difference in the mean length of stay in paediatric cardiac intensive care between the washed and unwashed red blood cell intervention groups (MD -0.30 days, 95% CI -4.32 to 3.72, 128 patients) ([Figure 6](#)).

### Re-hospitalisation rates

No trial reported data for this outcome.

### Biochemistry levels (outcome identified and added post-hoc)

### Restrictive transfusion trigger versus liberal transfusion trigger

[Cholette 2011](#) measured lactate levels. There was no difference in mean lactate level between the intervention arms at baseline (RR -0.10, 95% CI -0.73 to 0.53, 60 patients) and the 'peak' level during the initial 48-hour postoperative period (RR -0.10, 95% CI -0.81 to 0.61, 60 patients) ([Analysis 1.19](#)).

### Leukoreduced red cell transfusion versus non-leukoreduced red cell transfusion

No trial reported data for this outcome.

### Standard cardiopulmonary bypass prime versus non-standard cardiopulmonary bypass prime

Five trials measured this outcome (Chollette 2012; Hosking 1990; Liu 2007; Shimpo 2001; Swindell 2007). We did not undertake a meta-analysis due to clinical diversity in the nature of intervention.

### Lactate levels

Chollette 2012, Liu 2007, and Swindell 2007 measured lactate levels at different time points (Analysis 1.19). A difference was observed in mean lactate levels in two of these trials at different time points. In Liu 2007, there was a difference in lactate levels between the two groups favouring the processed packed red cells for the priming arm immediately after CPB with the clamp of arterial cannula (MD -1.60 mmol/L, 95% CI -2.65 to -0.55, 16 patients). In Swindell 2007, there was a difference in lactate levels on CPB prime prior to bypass (MD -2.00 mmol/L, 95% CI -0.94 to -3.06, 22 patients) and during re-warming at 28°C (MD -1.40 mmol/L, 95% CI -2.54 to -0.26, 22 patients). Comparisons for all three trials are available in Analysis 1.19.

### Sodium levels

Shimpo 2001 and Swindell 2007 measured sodium levels. Shimpo 2001 measured sodium levels before and after ultrafiltration in the patients who were treated with ultrafiltrated red blood cells only. Sodium levels remained within a clinically accepted normal range following receipt of ultrafiltrated red blood cells. Shimpo 2001 did not report the sodium levels for patients not receiving ultrafiltrated red blood cells, therefore, no further comparison of this outcome can be made.

In Swindell 2007, there was a difference in sodium levels on CPB prime prior to bypass (MD 4.00 mmol/L, 95% CI 0.94 to 7.06, 22 patients); during re-warming at 36°C (MD 3.10 mmol/L, 95% CI 0.44 to 5.76, 22 patients); and immediately after CPB with clamp of arterial cannula (MD 4.00 mmol/L, 95% CI 1.19 to 6.81, 22 patients). However, it should be noted that both sodium levels in the CPB circuit prime after line connection were not within normal clinical value ranges and would be of clinical concern. At the later time points (at 36°C during re-warming and immediately after CPB with clamp of arterial cannula) the sodium levels were within normal clinical levels. All comparisons for this trial are available in Analysis 1.20.

### Potassium levels

Shimpo 2001 and Swindell 2007 measured potassium levels. Shimpo 2001 measured potassium levels before and after ultrafiltration in the patients who were treated with ultrafiltrated red blood cells only. Potassium levels fell to within a clinically accepted normal range following receipt of ultrafiltrated red blood cells. Shimpo 2001 did not report the potassium levels for patients not

receiving ultrafiltrated red blood cells, therefore, no further comparison of this outcome can be made. In Swindell 2007, there was a difference in potassium levels on CPB prime prior to bypass (MD -5.50 mmol/L, 95% CI -6.31 to -4.69, 22 patients); at 28°C during re-warming (MD -1.90 mmol/L, 95% CI -2.71 to -1.09); and immediately after CPB with clamp of arterial cannula (MD -1.00 mmol/L, 95% CI -1.44 to -0.56, 22 patients) (Analysis 1.21).

### Blood glucose levels

In Hosking 1990 measured blood glucose levels. There was a difference in blood glucose level favouring the washed red blood cells at four time points: in the bypass priming solution prior to initiation of CPB (MD -282.00 mg/dL, 95% CI -315.06 to -248.94, 20 patients); 10 minutes after the initiation of CPB (MD -132.00 mg/dL, 95% CI -147.64 to -116.36, 20 patients); prior to separation from bypass (MD -134.00 mg/dL, 95% CI -168.44 to -99.56, 20 patients); and after the administration of protamine (MD -117.00 mg/dL, 95% CI -151.31 to -82.69, 20 patients). Two patients, one in each group, had a blood glucose concentration less than 60 mg/dL (outside that accepted normal range) in the pre-bypass period. The patient in the washed red blood cell group received two doses of glucose to correct the low glucose before the start of CPB. The other patient did not require treatment to correct their low glucose level before starting CPB. All comparisons for this trial are available in Analysis 1.22.

## DISCUSSION

The aim of this review was to evaluate the effects of red cell transfusion on mortality and morbidity on patients with congenital heart disease at the time of cardiac surgery. We identified 11 completed RCTs including 862 patients to evaluate red cell transfusion in three intervention areas: two trials explored transfusion triggers, two trials explored the benefit of leukoreduction and seven trials explored non-standard CPB. All trials were in neonatal or paediatric populations and there was a mix of cyanotic and acyanotic patients included across the trials.

### Summary of main results

The 11 studies included in this review were heterogeneous in terms of study population, interventions, outcomes and data quality. Therefore, we were unable to pool any data and the analysis is descriptive.

### Transfusion triggers

The two transfusion strategy trials showed no clear difference in mortality between the liberal and restrictive intervention arms (

Cholette 2011; Willems 2010). Cholette 2011 and Willems 2010 also showed no significant difference in the duration of mechanical ventilation or the duration of ICU stay between the intervention arms.

Willems 2010 showed no clear difference in the incidence of adverse cardiac events, acute lung injury and renal failure between intervention arms but showed an increase in the incidence of infection events in the liberal transfusion group. Both trials demonstrated no clear difference in postoperative haemorrhage rates between intervention arms (Cholette 2011; Willems 2010). As expected, both trials showed the liberal transfusion groups received more red cell transfusions. However, neither trial showed any significant difference in the transfusion of fresh frozen plasma or platelets between the two groups. Both trials showed the restrictive groups had a significantly lower haemoglobin concentration for the ICU period at the specific time points each trial measured.

The results suggest that restricting red blood cell transfusion is not detrimental to the survival of either acyanotic or cyanotic congenital cardiac patients. However, a restrictive transfusion trigger may prolong the ICU stay for the cyanotic population and a liberal transfusion trigger may increase the incidence of infection for the acyanotic population but both studies were inadequately powered to detect statistical differences in these clinical outcomes so conclusions are difficult.

## Leukoreduction

Leukoreduction aims to reduce the deleterious effects of leukocytes from allogeneic red cell transfusions. For duration of mechanical ventilation and length of intensive care, Komai 1998 (acyanotic population) showed a statistically non-significant shorter duration of mechanical ventilation and a statistically significant shorter length of ICU stay for the leukoreduced group. In contrast, de Vries 2004 (mixed cyanotic and acyanotic population) showed no statistically significant difference in duration of mechanical ventilation or ICU stay between groups. Most of the other main outcomes of interest were not reported by the two studies in this intervention (de Vries 2004; Komai 1998).

There were only two studies in this intervention area and they gave contrasting results with respect to the impact of leukoreduction. In addition, the patient populations were different. Therefore, it is difficult to draw definite conclusions for this intervention.

## Standard versus non-standard bypass

The aim of processing (washing) red blood cells that are added to the cardiopulmonary prime and returned to the patient is to reduce or eliminate any potential adverse effects of the altered biochemistry of stored allogeneic red blood cells.

Washing (pre-processing) red cells added to the CPB prime did not result in any clear difference in mortality for either of the two trials that reported mortality (Cholette 2012, early and late mortality;

Liu 2007, early mortality). Ultrafiltration (Shimpo 2001) and cell salvage (Ye 2013) did not result in any clear difference in mortality. Han 2004 (bloodless bypass prime) did not report mortality.

Washing bypass prime red cells did not result in any clear difference in adverse events of infection, thrombosis, arrhythmias and postoperative bleeding in the one trial that reported all of these outcomes (Cholette 2012). Cell salvage did not result in any clear difference in respiratory morbidity but the incidence of an increase in serum creatinine more than two-fold 72 hours after the operation was significantly lower in the cell salvage group (Ye 2013). No patients in either group required dialysis postoperatively.

Unsurprisingly, a bloodless bypass prime showed lower haematocrit levels during bypass (statistical significance not reported; Han 2004). Processing prime red blood cells significantly increased haematocrit at 10 minutes during bypass and at the end of bypass (Liu 2007). Cell salvage significantly increased the haematocrit level on the first postoperative day but not at any other time points at baseline, during bypass or just after bypass (Ye 2013).

Washing bypass prime red cells did not result in any clear differences in duration of mechanical ventilation or ICU stay (Cholette 2012). Cell salvage did not result in any clear difference in duration of mechanical ventilation (Ye 2013). The study did not report length of ICU stay. Ultrafiltration resulted in a significantly reduced duration of mechanical ventilation and ICU stay (Shimpo 2001).

The different methods of washing (processing) bypass prime red cells resulted in significant reductions in potassium levels at various time points in two studies; Liu 2007 before CPB and Swindell 2007 prior to red cell addition to the bypass prime, throughout bypass and immediately post bypass. Ultrafiltration also reduced potassium levels with Shimpo 2001 reporting ultrafiltered priming blood had a significantly lower potassium level when compared with pre-ultrafiltration.

Lactate levels were variably affected by the washing (processing) techniques. Liu 2007 showed processed packed red blood cells with continuous autologous transfusion system (CATS) had significantly higher lactate levels before CPB and lower lactate levels at 10 minutes during and at the end of CPB. However, Swindell 2007 showed significantly lower lactate levels in the washed packed red blood cells prior to addition to the bypass prime but no significant difference in lactate levels between the two groups during bypass apart from at 28°C re-warming when the unwashed group showed a significantly higher lactate level. Cholette 2012 reported no significant difference in either ICU admission lactate or peak ICU lactate levels between the two groups.

Overall, the studies were too heterogeneous in terms of patient populations and exact intervention types to make accurate conclusions about the impact of washing (processing) red cells. It does appear that washing and ultrafiltration reduces potassium levels. The data on lactate are less clear.

The important outcome for a bloodless bypass prime was intraoperative cerebral oxygen saturations, as reported by one trial (Han



2004). The crystalloid prime group showed significantly lower cerebral oxygen saturations when compared with blood containing prime three minutes after initiating bypass and 15 minutes after the start of re-warming. This may suggest excessive haemodilution in the bloodless bypass prime but the clinical significance of this is unknown as the trial did not specifically report neurological outcomes post surgery.

## Overall completeness and applicability of evidence

The trials included in this review are insufficient to address the objectives of our systematic review. There are gaps in the evidence base in terms of patient population (we found no trials in adults), interventions (no trials examined the interventions of volumes of red cell transfusion, whole blood versus packed red cells or the age of red cells transfused), and the completeness of outcomes measured and reported by the included trials. Our primary outcome was reported by only five included trials. No trials reported data for two outcomes: stroke and re-hospitalisation rates. The number of trials providing data for individual outcomes ranged from one (thromboembolism) to seven (duration of mechanical ventilation and biochemistry levels). The outcome of biochemistry levels was added post hoc as it became clear during data extraction (and following consultation with clinical colleagues) that the outcome was of clinical significance to this review question, but had been overlooked when we prepared the protocol.

The trials that do exist are not in sufficient numbers or homogeneity to pool results for any of the outcomes of interest to this review. This may limit the applicability of the evidence within this review.

## Quality of the evidence

Overall, it was difficult to assess the quality of the evidence accurately as much information was lacking; many elements of trial quality in each trial were marked as having an unclear risk of bias. Attrition was low across all included trials. We assessed five trials as having elements of high risk of bias on method of randomisation (Komai 1998), method of allocation concealment (de Vries 2004), blinding of study personnel (Cholette 2011; Cholette 2012; Willems 2010), and blinding of outcome assessors (Cholette 2012). Blinding would be difficult to achieve for some interventions within this review. Although, as none of the outcomes were patient reported, we did not deem blinding of participants to be an important risk of bias.

The sample size of the 11 included trials was generally small. Only four trials had greater than 50 patients in each treatment arm included in the analysis of outcome data (Cholette 2012; Shimpo 2001; Willems 2010; Ye 2013). This may well reflect the nature of the condition of interest to this review, but does limit the statistical

power of these trials to detect differences in outcomes of interest in this clinical area.

As has already been noted, the substantial clinical diversity in the included trials and the variability in outcome data reported has prevented any pooling of outcome data, thus the consistency (or inconsistency) of results across the included trials is difficult to ascertain. Addressing such variability should be a key component of future research in this area.

## Potential biases in the review process

We identified no biases in the review process. The strengths of this review lie in the robust and comprehensive methodology employed to find and assess all relevant trials. We have followed standard Cochrane methods for data extraction and results analysis with reference to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and have referred to a statistician where necessary. We have had a clinician and methodologist working on all stages, independently of each other to control any bias that ensues due to clinical or systematic review methodology knowledge. When we were limited by a lack of reporting data to allow inclusion and assessment of trials, we successfully contacted authors directly to obtain the necessary data.

## Agreements and disagreements with other studies or reviews

To date, as far as we are aware, there have been no other systematic reviews specifically examining the effects of red cell transfusion on mortality and morbidity on the congenital heart disease population at the time of cardiac surgery (Dorée 2010). Guzzetta 2011 reviewed the risks and benefits of red cell transfusion and concluded that the efficacy of red cell transfusion has never been equivocally shown even in well-designed trials and further well-designed trials are needed in this heterogeneous population. Our review would appear to agree with this conclusion.

# AUTHORS' CONCLUSIONS

## Implications for practice

Transfusion practice in children with congenital heart disease is likely to be firmly based on individual centre practice, as there are no widely accepted guidelines for transfusion practice in this patient population. There is no high-quality evidence on which to provide guidelines for transfusion practice in this population. This is not surprising as congenital heart disease affects small numbers of people with a previously high mortality.

Congenital heart disease is now associated with a low mortality. Although cardiac surgery carries inherent risks in this population,

the estimated effects on postoperative and longer-term mortality were imprecise in the trials assessing postoperative restrictive versus liberal transfusion triggers, and were consistent with benefit and harm. We were unable to determine whether transfusion plays a role in reducing morbidity. This review has found few studies to assess the impact of red cell transfusion on children undergoing cardiac surgery for congenital heart disease. These studies provide limited evidence, and the trials were underpowered for clinical outcomes.

## Implications for research

This review highlights gaps and deficiencies in the current evidence base. Future trials need to be designed correctly: adequately

powered, age specific (neonates, paediatrics and adult age groups) and specific for the type of congenital heart disease (cyanotic and acyanotic groups). The adult congenital heart disease population is one of the fastest growing populations in the UK but this review has not found any studies assessing the impact of red cell transfusion in this particular population group. These are all important considerations for future research.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Cholette 2011

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: full</p> <p>Setting: URM, Rochester, NY, USA</p> <p>Number of centres: 1</p> <p>Dates of trial (start and end): August 2006 to September 2009</p> <p>Follow-up: until hospital discharge</p> <p>Number of patients randomised: 31 in each group</p> <p>Number of patients analysed (primary outcome): 30 in each group</p>
Participants	<p>Inclusions: neonates and children presenting for elective partial or total cavopulmonary connection (bidirectional Glenn or Fontan procedures). The children had single ventricle physiology (including hypoplastic left heart syndrome, double inlet left ventricle, tricuspid atresia, pulmonary atresia, double outlet right ventricle, Ebstein's anomaly, unbalanced atrioventricular septal defect, hypoplastic right ventricle variant)</p> <p>Age: restrictive group mean 27 months (SD 23), liberal group mean 32.5 months (SD 27)</p> <p>Gender (M/F): 34/26</p> <p>Exclusions: those in whom consent could not be obtained</p> <p>Statistically significant baseline imbalances between the 2 groups: no</p>
Interventions	<p>2 groups: restrictive and liberal</p> <p>Intervention arm: restrictive transfusion strategy = 10 mL/kg of leukoreduced, irradiated red blood cells for any Hb &lt; 9.0 g/dL accompanied by clinical findings suggestive of symptomatic anaemia for 48 hours post operation</p> <p>Comparator arm: liberal transfusion strategy = 10 mL/kg of leukoreduced, irradiated red blood cells for Hb &gt; 13.0 g/dL regardless of whether there was a clinical indication for transfusion for 48 hours post operation</p> <p>Transfusions were given within 1 hour of reaching Hb threshold</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>mean and peak arterial lactate level during initial 48 hours post operation</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>C(a-v) O<sub>2</sub>, C(a-c) O<sub>2</sub></li> </ul> <p>Clinical outcomes:</p> <ul style="list-style-type: none"> <li>length of mechanical ventilation</li> <li>length and dose of vasoactive agent administration</li> <li>PCICU and hospital length of stay</li> <li>mediastinal chest tube drainage</li> <li>volume of crystalloid and albumin infused during the study period</li> </ul> <p>Outcome assessment points: on PCICU admission and at every 4 hours for 48 hours</p>
Notes	<p>Funding: University of Rochester Strong Children's Research Centre Research Development Award 2006-2007 (JMC)</p> <p>Study duration: the study was only carried out for 48 hours post operation in PCICU</p>



	<p>and then transfusion strategies were relaxed. The patients stayed in PICU for a mean of 6.6 (SD 6.4) days (restrictive) and 5.4 (SD 3.3) days (liberal) so were in PICU for longer than the defined study duration. As stated above, a significant number of children in both groups were transfused after the 48-hour period. Significantly, the mean Hb in the groups were not markedly different and it may be argued that a mean Hb of 11.1 g/dL is not truly restrictive</p> <p>Compliance: there was 100% compliance with the trial protocol and the protocol was not suspended during the trial period</p> <p>Sample size calculation: Chollette 2011 determined that 29 patients would be needed per group to have 80% power to reject the null hypothesis that the 2 treatment arms would be equivalent in terms of mean and peak lactate levels. The type 1 error rate was set at 0.05. 60 patients (30 in each group) were analysed, so the calculated requisite numbers were attained. However, the study was not powered to assess for clinical outcome differences, only lactate differences</p>
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<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation (block size 8) was used to randomise into either transfusion strategy. Insufficient information about sequence generation process to permit judgement of 'Yes' or 'No'
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinical staff and patient's families were aware of transfusion group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessor not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. 2 patients (3% of patients in this trial) who were randomised to the study were excluded, 1 patient from each group. Both patients could not have surgery: 1 patient could not be endotracheally intubated and 1 patient had bleeding complications before going onto CPB. The authors did not include this patient's data in their outcome analyses. No other patient dropped out of the study or were lost to follow-up

**Cholette 2011** (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes defined in the methods section were reported on in the results section
Other bias	Low risk	None reported

**Cholette 2012**

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: full</p> <p>Setting: UPMC, Rochester, NY, USA</p> <p>Number of centres: 1</p> <p>Dates of trial (start and end): October 2008 to September 2010</p> <p>Follow-up: not clearly stated, but duration of hospital stay was up to 78 days</p> <p>Number of patients randomised: 81 in each group</p> <p>Number of patients analysed (primary outcome): 64 in each group</p> <p>Only those randomised patients who received a transfusion on study entrance were included in the analysis of outcomes. No patients were lost to follow-up</p>
Participants	<p>Inclusions: Children up to 18 years presenting to the UPMC for cardiac surgical repair/palliation with CPB</p> <p>The surgical procedures undergone by the study patients included stage 1 palliation; arterial switch operation; bidirectional Glenn; tetralogy of Fallot repair; atrial, ventricular or atrioventricular septal defect repair; aortic arch reconstruction and Fontan</p> <p>Age: washed group: median 6 months (IQR 3 days to 17 years); unwashed group: median 7 months (IQR range 2 days to 17 years)</p> <p>Gender (M/F): washed group: 63/18; unwashed group: 64/17</p> <p>Exclusions: patent ductus arteriosus repair, if parent/guardian did not speak English, if consent could not be obtained or patient participating in another clinical trial</p> <p>Statistically significant baseline imbalances between the 2 groups: no</p>
Interventions	<p>2 groups: washed and unwashed</p> <p>Intervention arm: all red cell and platelets transfusions were washed after storage for the duration of the hospital stay. The protocol could be temporarily suspended at the discretion of the attending physician if the time taken to wash blood products (2 hours for platelets; 30 minutes for red blood cells) interfered with patient care</p> <p>Comparator arm: all red cell and platelet transfusions were prepared according to standard protocol at the UPMC for the duration of the hospital admission</p> <p>The study transfusion strategy was initiated for the operating room and maintained until hospital discharge. All blood products were leukoreduced before storage, irradiated and ABO blood group identical, without restrictions on storage age</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>12 hour post CPB IL-6:IL-10 ratio</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>mortality up to 30 days</li> <li>severe adverse events: cardiac, thromboembolism, infection, haemorrhage</li> <li>red blood cell units and other blood products transfused to discharge</li> <li>duration of mechanical ventilation</li> </ul>

	<ul style="list-style-type: none"><li>• duration of ICU stay</li></ul> <p>In addition, the following outcomes were reported by the trial (but not included in this review): inotropic/vasopressor hours, central venous line duration, mediastinal tube days, antibiotics, PCICU admission lactate, peak lactate, volume, highest white blood count postoperatively on days 0-2, PCICU complication and ECMO duration</p>	
Notes	<p>Funding: Strong Children’s Research development award from URM - Department of Pediatrics, National Institute of Environmental Health Sciences/National Institute of Health (ESO1247) and the National Heart Lung and Blood Institute/National Institute of Health (HL100051, HL095467)</p> <p>ClinicalTrials.gov record number: NCT00693498</p> <p>Protocol violations: 1 in the washed group (a neonate who received 1 unwashed platelet transfusion) and 2 in the unwashed group (both patients required ECMO and all products for ECMO were washed to prevent hyperkalaemia)</p> <p>Sample size calculation: <a href="#">Chollette 2012</a> calculated that a sample of 64 patients per group would provide 80% power to detect a relatively small group difference of 2 units (one half of SD) of the mean IL-6:IL-10 ratio. 64 patients were included in each group making the study adequately powered for differences in IL-6:IL-10 ratios. However, these study numbers were not large enough to power the study to test for clinical outcomes</p>	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote (p. 291): “... block randomisation was used to randomise to the unwashed or washed transfusion strategy”. Insufficient information about sequence generation process to permit judgement of ‘Yes’ or ‘No’
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Email communication with the main author identified that no one involved in patient care could be blinded to treatment allocation due to packaging differences of the blood products that were not allowed to be concealed under FDA, New York state and hospital regulations. The blood bank sent blood appropriate to the allocation (washed or unwashed). When blood was not hanging the treatment allocation was not obvious and the clinician would not be aware of trial assignment

Blinding of outcome assessment (detection bias) All outcomes	High risk	Email communication with the main author identified that outcome assessment was determined from inpatient notes from the PCICU attending physician and cardiothoracic surgery nurse practitioner: both of whom were not blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors report that there were no missing outcome data: no patients were lost to follow-up and data were analysed by both ITT and per-protocol principles. 34 randomised patients (17 from each treatment group) did not receive a transfusion and were thus excluded from the per-protocol analysis 6 patients were excluded following randomisation: 3 because shunts were performed off by-pass, 2 because surgical palliation was not offered and 1 patient in whom surgery was not performed. These patients did not receive a transfusion and were excluded from all outcome analyses
Selective reporting (reporting bias)	Low risk	The trial protocol is available and all outcomes pre-specified (IL-6:IL-10 ratio and wide-range C-reactive protein levels) in the protocol have been reported in this trial as pre-specified
Other bias	Low risk	None reported

#### de Vries 2004

Methods	Type of study: parallel RCT Type of publication: full Setting: University Hospital Groningen, the Netherlands Number of centres: 1 Dates of trial (start and end): not stated Follow-up: until hospital discharge Number of patients randomised: 25 in each group Number of patients analysed (primary outcome): 25 in each group
Participants	Inclusions: children who were undergoing congenital open-heart surgery. Procedures selected were correction of tetralogy of Fallot, simple closure of ventricular septal defect, correction of atrioventricular septal defect, arterial switch operation of transposition of the great arteries and completion of the Fontan procedure Age: filtration group: median 13 months (IQR 2 to 31.5), control group: median 6

	<p>months (IQR 1 to 28.5)</p> <p>Gender: not reported</p> <p>Exclusions: not stated</p> <p>Statistically significant baseline imbalances between the groups: no</p>
Interventions	<p>2 groups: filtration and control</p> <p>After CPB and disconnection of the system, the residual blood in the heart-lung machine was collected in a transfusion bag and re-transfused in the child during wound closure and the first 2 hours in the ICU</p> <p>Intervention arm: filtration group: the re-transfused blood was filtered with one leukoreduction filter (Pall RS 1, Pall, Portsmouth, UK) for each patient</p> <p>Comparator arm: control group: no filtration of re-transfused blood</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>• PaO<sub>2</sub> on the first postoperative day</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>• leukocyte counts after induction of anaesthesia and on the first 4 postoperative days</li> <li>• platelet counts and PaO<sub>2</sub> after induction of anaesthesia and after arrival on the ICU (in addition to primary outcome)</li> </ul> <p>In 10 children: additional blood samples were taken from the residual heart-lung machine blood. In these samples, leukocyte and platelet counts and levels of Hb and elastase as a measure of leukocyte activation, were determined</p>
Notes	<p>Funding: not stated</p> <p>Study objective: the study was designed to examine the effect of leukoreduction of residual heart-lung machine blood on postoperative oxygenation and circulating leukocyte counts in children undergoing congenital heart surgery</p>

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	High risk	Unsealed envelopes (information direct from trialist by email)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported so insufficient information to permit judgement of 'Yes' or 'No'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information to permit judgement of 'Yes' or 'No'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data identified

Selective reporting (reporting bias)	Low risk	All outcomes defined in the methods section were reported on in the results section
Other bias	Low risk	None reported

**Han 2004**

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: full</p> <p>Setting: Seoul National University, Seoul, Korea</p> <p>Number of centres: 1</p> <p>Dates of trial (start and end): not reported</p> <p>Follow-up: during operative period</p> <p>Number of patients randomised: 18 in each group</p> <p>Number of patients analysed (primary outcome): 17 in blood-containing prime group, 18 in crystalloid group</p>
Participants	<p>Inclusion: children weighing 8-12 kg who were scheduled for elective surgical repair of ventricular or atrial septal defect</p> <p>Age: intervention group: median 19.5 months (IQR 10 to 29); control group: median 22 months (IQR 9 to 35)</p> <p>Gender (M/F): 20/15</p> <p>Exclusion: children with a preoperative haematocrit &lt; 35%, children who needed pre-operative inotropic support or children with a known neurological problem</p>
Interventions	<p>2 groups: blood-containing prime group or crystalloid. The priming volume was 600 mL for both groups</p> <p>Intervention arm: packed red blood cells were added to the prime to achieve a haematocrit of 20% on initiation of CPB</p> <p>Control arm: pump prime consisted of Normosol</p> <p>Both groups had perfusion maintained at 150 mL/kg/minute with moderate hypothermia and alpha stat management. Conventional and modified ultrafiltrations were performed. Intraoperative cell salvage was performed in the control group and salvaged red cells were re-infused after surgery</p> <p>During CPB, transfusion was initiated if rSO<sub>2</sub> decreased below 20% of pre-bypass value. After finishing modified ultrafiltration, transfusion was performed if haematocrit was &lt; 28%</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>● rSO<sub>2</sub> (assumed to be primary outcome but not specifically stated)</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>● mean arterial pressure</li> <li>● nasopharyngeal temperature</li> <li>● haematocrit</li> <li>● arterial blood gas measurement</li> <li>● arterial oxygen content</li> </ul>

Notes	Funding: not reported Study objective: the study was performed to compare the effect of bloodless CPB prime with that of red blood cell-containing prime on rSO <sub>2</sub> value, as measured by near infra-red spectroscopy 1 patient in the crystalloid group was excluded from analysis as after initiation of CPB, rSO <sub>2</sub> decreased to 53% of that before bypass with a haematocrit of 13%. Red blood cells were transfused and rSO <sub>2</sub> improved within seconds	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Computer-generated table
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported but patients were asleep so unlikely to know but anaesthetist, surgeon and perfusionist likely to know. Insufficient information provided to make definite judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information provided to make definite judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient was excluded but reasons given. 1 patient (3% of patients in this trial) in the intervention group was excluded for clinical reasons. After initiation of CPB, the rSO <sub>2</sub> saturations levels dropped to an unacceptable level and red cell transfusion was required. rSO <sub>2</sub> saturations improved within seconds. The authors did not include this patient's data in their outcome analyses. No other patients were excluded or withdrew from the trial
Selective reporting (reporting bias)	Unclear risk	The trial did not define the outcomes they were interested in; therefore there is insufficient information to identify whether there was reporting bias in these trials
Other bias	Unclear risk	None reported. It would be difficult to rule out as very little methodological detail was provided in the trial report

**Hosking 1990**

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: full</p> <p>Setting: Mayo Clinic, Rochester, MN, USA</p> <p>Number of centres: 1</p> <p>Dates of trial (start and end): not reported</p> <p>Follow-up: intraoperatively</p> <p>Number of patients randomised: 10 in each group</p> <p>Number of patients analysed (primary outcome): 10 in each group</p>
Participants	<p>Inclusion: infants weighing &lt; 10 kg scheduled for cardiac surgical procedures (acyanotic and cyanotic)</p> <p>Age: washed red blood cell group: mean 7 months (SD 4.9); packed red blood cells: mean 8.3 months (SD 4)</p> <p>Gender: not stated</p> <p>Exclusion: infants with diabetes mellitus or other endocrine disturbances that could result in an abnormal response to glucose</p>
Interventions	<p>2 groups: washed red blood cells and packed red blood cells</p> <p>Intervention arm: washed packed red blood cells (with isotonic saline to decrease blood glucose concentrations to 30-60 mg/dL) added into CPB prime to yield a haematocrit of 25% during CPB</p> <p>Comparator arm: packed red blood cells added into CPB prime to yield a haematocrit 25% during CPB</p> <p>Red blood cells were suspended in AS-1 preservative solution (adenine-glucose-mannitol-saline) and added into the CPB prime prior to the child going onto CPB and intra-operatively to replace intraoperative losses</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>not stated</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>blood glucose concentrations after induction, prior to initiation of CPB, 10 minutes after initiation of CPB, 10 minutes prior to separation from CPB and after protamine administration</li> </ul>
Notes	Funding: not reported

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information was provided to enable an assessment of random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment



## Hosking 1990 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis of outcome data and no patients were lost during follow-up
Selective reporting (reporting bias)	Unclear risk	The trial did not define the outcomes they were interested in; therefore, there is insufficient information to identify whether there was reporting bias in these trials
Other bias	Unclear risk	None reported. It would be difficult to rule out as very little methodological detail was provided in the trial report

## Komai 1998

Methods	Type of study: parallel RCT Type of publication: full Setting: Department of Thoracic and Cardiovascular Surgery, Wakayama Medical College, Wakayama, Japan Number of centres: 1 Dates of trial (start): from April 1991. End date not reported Follow-up: duration of ITU stay Number of patients randomised: 24 in leukocyte removal arm, 22 in control arm Number of patients analysed: 24 in leukocyte removal arm, 22 in control arm
Participants	Inclusion: undergoing elective open-heart surgery for radical correction of ventricular septal defect Age: leukoreduction group: median 22.5 months (range 7 months to 10 years); control group: median 22.5 months (range 3 months to 8 years) Gender (M/F): 25/21 Exclusion: not reported but no patient had been intubated or on catecholamines before the operation Statistically significant baseline imbalances between the groups: no
Interventions	2 groups: surgical technique and anaesthesia were uniform for both groups. For both groups the priming fluid of the CPB circuit consisted of crystalloid solution (Ringer's lactate), colloid solution (albumin or plasma protein fraction) and banked blood. The number of blood units used was determined individually to give an estimated haematocrit level during bypass of around 25% Intervention arm: leukoreduction group: a leukoreduction filter (Pall RC100 or 400,

	Pall Biomedical, Glen Cove, USA) was used for priming, as well as in every supplement of banked blood used during and after the operation Comparator arm: control group: banked blood was primed without using any leukoreduction technique	
Outcomes	Primary: <ul style="list-style-type: none"><li>● outcome not defined</li></ul> Other outcomes: <ul style="list-style-type: none"><li>● perioperative changes in <math>P_p</math>:<math>P_p</math> and <math>P_s</math> measured simultaneously just before and after CPB to calculate the percentage decrease in <math>P_p/P_s</math></li><li>● respiratory index after intracardiac repair</li><li>● intubation time and duration of stay in the ICU</li><li>● blood analysis and blood chemistry test: white blood cell count, platelet count, creatinine, total bilirubin, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase 1 week before, 1 day after and 7 days after operation</li></ul>	
Notes	Funding: not reported Study objective: the trial was designed to determine the clinical effect on lung function of reducing allogeneic leukocytes for children with ventricular septal defects undergoing open-heart surgery	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Used an alternation method: this data was provided through direct email contact with the authors
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis of outcome data and no patients were lost during follow-up
Selective reporting (reporting bias)	Unclear risk	The trial did not define the outcomes they were interested in; therefore, there is insufficient information to identify whether there was reporting bias in these trials

Other bias	Low risk	None reported
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**Liu 2007**

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: full</p> <p>Setting: Fuwai Hospital, Beijing, China</p> <p>Number of centres: 1</p> <p>Dates of trial (start and end): May 2005 to December 2006</p> <p>Follow-up: operative period</p> <p>Number of patients randomised: 8 in each group</p> <p>Number of patients analysed: 8 in each groups</p>
Participants	<p>Inclusion: neonates with congenital heart disease undergoing cardiac surgery with CPB. Diagnoses were transposition of the great arteries with ventricular septal defect and patent ductus arteriosus (13 patients) or interrupted aortic arch with patent ductus arteriosus (3 patients)</p> <p>Age: processed packed red cells group: mean 14 days (SEM 3); unprocessed packed red blood cells: mean 12 days (SEM 4)</p> <p>Gender (M/F): not clearly reported</p> <p>Exclusions: not reported</p> <p>Statistically significant baseline imbalances between the groups: no</p>
Interventions	<p>2 groups: processed and unprocessed packed red blood cells</p> <p>Intervention arm: received processed packed red blood cells before priming with CATS (Fresenius, Bad Homburg, Germany)</p> <p>Comparator arm: received unprocessed packed red cells for priming</p> <p>The washing procedure by CATS lasted approximately 7 minutes and used 1000 mL of 0.9% sodium chloride wash solution</p> <p>All packed red blood cells were acquired from a standard donor bank</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>not stated</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>series laboratory and clinical parameters of haematocrit, blood potassium, blood glucose, blood lactate, acid-base and total priming volume of packed red blood cells. Levels were measured pre-processing (i.e. baseline for both groups), post processing (in intervention arm only), at 10 minutes during CPB and at the end of CPB</li> </ul>
Notes	<p>Funding: not reported</p> <p>Study objective: the objective of the trial was to compare the effect of unprocessed and processed packed red blood cells with CATS on neonates undergoing corrective cardiac surgery</p>

***Risk of bias***

Bias	Authors' judgement	Support for judgement
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**Liu 2007** (Continued)

Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The blinding of patients and personnel was not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The blinding of outcome assessors was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were included in the analysis and no patients were lost during follow-up
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methods are reported in results
Other bias	Low risk	None reported

**Shimpo 2001**

Methods	Type of study: parallel RCT Type of publication: full Setting: Edobashi Tsu, Japan Number of centres: 1 Dates of trial (start and end): not reported Follow-up: not stated Number of patients randomised: 50 in each group Number of patients analysed (primary outcome): 50 in each group
Participants	Inclusion: children undergoing cardiac operations to correct congenital heart defects Age: ultrafiltration group: mean 9.7 months (SD 1.8); control group: mean 10.6 months (SD 1.9) Gender (M/F): ultrafiltration group: 15/12; control group: 11/12 Exclusion: not stated
Interventions	2 groups Intervention arm: ultrafiltration group: stored packed red blood cells priming solution was treated with ultrafiltration before CPB was initiated Control arm: no - ultrafiltration group.

Outcomes	Primary: <ul style="list-style-type: none"><li>● not stated</li></ul> Other outcomes: <ul style="list-style-type: none"><li>● electrolytes</li><li>● NH<sub>3</sub></li><li>● prekallikrein</li><li>● kininogen</li><li>● bradykinin</li><li>● blood gases before and after ultrafiltration</li></ul>	
Notes	Funding: not reported	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	No information was provided to enable an assessment of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote (p. 52): "Just before setting up the operating room, the randomisation process was performed. Only the perfusionist was informed which method to use"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (p. 52): "Just before setting up the operating room, the randomisation process was performed. Only the perfusionist was informed which method to use"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (p. 52): "Just before setting up the operating room, the randomisation process was performed. Only the perfusionist was informed which method to use"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis of outcome data and no patients were lost during follow-up
Selective reporting (reporting bias)	Unclear risk	The trial did not define the outcomes they were interested in; therefore, there is insufficient information to identify whether there was reporting bias in these trials
Other bias	Unclear risk	None reported. It would be difficult to rule out as very little methodological detail was provided in the trial report

**Swindell 2007**

Methods	Type of study: parallel RCT Type of publication: full Setting: Birmingham Children's Hospital, Birmingham, UK Number of centres: 1 Dates (start and end): January 2005 to May 2006 Follow-up: not stated but measurements taken intraoperatively Number of patients randomised: 11 in each group Number of patients analysed (primary outcome): 11 in each group
Participants	Inclusion: infants (< 1 year old) and neonates undergoing CPB for complex congenital heart surgery Diagnoses were hypoplastic left heart syndrome (12 patients), multiple complex defects (5 patients), transposition of the great arteries (3 patients), pulmonary atresia and ventricular septal defect (1 patient), hypoplastic aortic arch (1 patient). The operations they underwent were modified Norwood Stage 1 (12 patients), cavo-pulmonary shunt (4 patients), arterial switch (3 patients), aortic arch repair (2 patients), pulmonary atresia repair (1 patient) Age: washed group: mean 45 days (range 1 to 180); unwashed group: mean 62 days (range 2 to 300) Weight: washed group: mean 4.2 kg (range 2.62 to 8.2); unwashed group: mean 4.0 kg (range 2.4 to 8.3) Gender (M/F): 12/10 Exclusion: not reported Statistically significant baseline imbalances between groups: not stated but control group have a higher mean age: 62 days versus 45 days
Interventions	2 groups: unwashed and washed All patients in the study received irradiated red cells as they had, or were suspected to have had, a syndrome associated with immunodeficiency as stated in the transfusion guidelines for Birmingham Children's Hospital Intervention arm: washed received the processed volume from 2 units of irradiated pre-washed in a cell-saver before addition to the CPB circuit prime. They received 2 units to compensate for the volume loss during processing Comparator arm: unwashed received 1 unit of unwashed irradiated red cells in the CPB circuit prime. They also received a second unit of unwashed irradiated red cells as required during CPB
Outcomes	Primary: <ul style="list-style-type: none"><li>• potassium and lactate levels in the irradiated red cells and inpatient samples</li></ul> Other outcomes: <ul style="list-style-type: none"><li>• sodium concentrations</li></ul> Samples were taken before addition to the prime (for the intervention group this meant pre and post washing), after connection of lines and 5 minutes of re-circulation in bypass prime, from patient arterial blood prior to bypass, bypass circuit sample after start of bypass, at 28°C during cooling then re-warming, then at 36°C after re-warming. A final sample was taken from patient arterial blood immediately after bypass and clamping of arterial cannula

Notes	Funding: not reported Study objective: the study aimed to identify whether cell-saver washing of irradiated red cells prior to transfusion reduced potassium and lactate levels in the donor blood. In addition, aimed to identify whether transfusion of washed red cells prevented hyperkalaemia and hypercalcaemia in the serum of neonates and infants undergoing open-heart surgery. In an appendix at end of paper, a conference discussion was reported and the issue of the need to give all of this patient population irradiated red cells. The authors agree that not all of their patients may have needed irradiated red cells so the issue of high potassium and lactate levels may not be relevant to all	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported but theatre staff unlikely to be blinded as washing equipment would be visible to all
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis of outcome data and no patients were lost during follow-up
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methods are reported in results
Other bias	Low risk	None reported

Methods	<p>Type of study: parallel RCT</p> <p>Type of publication: subgroup analysis of TRIPICU study (<a href="#">Lacroix 2007</a>)</p> <p>Setting: tertiary care paediatric ICUs in Belgium, Canada and the USA</p> <p>Number of centres: 7 (TRIPICU study had 19 participating centres)</p> <p>Dates: November 2001 to August 2008 (information from original TRIPICU publication)</p> <p>Follow-up: 28 days post randomisation</p> <p>Number of patients randomised: 63 in restrictive group, 62 in liberal group</p> <p>Number of patients analysed (primary outcome): 63 in restrictive group, 62 in liberal group</p>
Participants	<p>125 patients (represented 19.6% of all the TRIPICU patients)</p> <p>Inclusion: subgroup of paediatric patients post cardiac surgery from the TRIPICU study. The patients had undergone cardiac surgery or cardiac catheterisation. All patients with at least 1 Hb concentration <math>\leq 9.5</math> g/dL within the first 7 days after paediatric ICU admission were considered for inclusion</p> <p>The most common surgeries were coarctation repair (13 patients), ventricular septal defect repair (16 patients), repair of tetralogy of Fallot (24 patients), repair of atrioventricular canal defect (11 patients), mitral valve surgery (8 patients), Rastelli procedure (8 patients), arterial switch procedure (5 patients)</p> <p>Age: restrictive mean 31.4 months (SD 38.1), liberal mean 26.4 months (SD 39.1)</p> <p>Gender (% male): restrictive group: 57, liberal group: 57</p> <p>Weight: restrictive mean 11.5 kg (SD 10.4), liberal mean 10.0 kg (SD 8.5)</p> <p>Exclusion: specific to cardiac surgery subgroup were age &lt; 28 days, patients with cyanotic heart disease (with right-to-left shunt) who had a palliative intervention (procedures such as Norwood, Glenn, Fontan or a shunt between a systemic and a pulmonary artery were considered palliative)</p> <p>Statistically significant baseline imbalances between groups: no</p>
Interventions	<p>2 groups: pre-storage leukoreduced allogeneic red cell units were transfused when transfusion thresholds were reached</p> <p>Intervention arm: restrictive: transfusion threshold 7.0 g/dL</p> <p>Comparator arm: liberal: transfusion threshold 9.5 g/dL</p> <p>Transfusion strategies were applied for up to 28 days post randomisation</p> <p>The research protocol allowed temporary suspension during active blood loss, surgery, severe hypoxaemia or haemodynamic instability</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>proportion of patients who developed or had progression of MODS</li> </ul> <p>Other outcomes:</p> <ul style="list-style-type: none"> <li>markers of severity of MODS (highest number of organ dysfunction per patient and paediatric Logistic Organ Dysfunction Score)</li> <li>nosocomial infections</li> <li>oxygenation markers</li> <li>duration of mechanical ventilation</li> <li>length of ICU stay</li> <li>number of red cell transfusion reactions</li> <li>28-day mortality</li> <li>vasoactive drugs and corticosteroid use</li> </ul>



Notes	<p>Funding: supported in part by grants 84300 and 130770 from the Canadian Institutes of Health Research (CIHR) and Grant 13904 from the Fonds de la Recherche en Sante du Quebec</p> <p>Study objective: this study aimed to determine the impact of a restrictive versus a liberal transfusion strategy on new or progressive multiple organ dysfunction in children post cardiac surgery. It is difficult to determine from this paper the exact methodology used but this is well documented in the original TRIPICU paper</p> <p>Study sample size: <a href="#">Willems 2010</a> was a subgroup analysis of the larger RCT, the TRIPICU study (<a href="#">Lacroix 2007</a>). The original TRIPICU paper estimated they would need to enrol 626 patients to detect an absolute reduction of 10% in the risk of new or progressive organ dysfunction in the group treated according to the restrictive transfusion strategy, with an overall one-sided alpha of 5% and a power of 90%. 637 patients were included in the analysis giving the TRIPICU study the requisite numbers to attain the desired power. As <a href="#">Willems 2010</a> is a subgroup analysis the power calculations of the main trial are not relevant. The subgroup analysis was based on 125 patients: the paper states that the power of this subgroup analysis was not optimal and the number of patients was too small to permit any conclusions. The study reports results for the 125 patients it randomised (ITT analysis)</p> <p>Protocol adherence: 10 patients did not reach their pre-defined criteria for good protocol adherence (80%) and these patients were excluded from a per-protocol analysis performed for their primary outcome (MODS). The results of the ITT and per-protocol analysis differed slightly, but neither analysis resulted in a difference in the number of patients developing or experiencing a worsening of MODS between the 2 study treatment arms</p> <p>The actual protocol adherence rates were not stated for other outcomes and a per-protocol analysis was similarly not reported for any other outcome. We have used the ITT data the study reports in our review</p> <p>In addition, 7 patients in the restrictive group and 1 in the liberal group were suspended temporarily from the transfusion protocol (<math>1.1 \pm 0.4</math> days and 1.0 days, respectively): during this time, 7 red cell transfusions were given in the restrictive group and 1 red cell transfusion in the liberal group. All products received while suspended were accounted for in the outcome analysis</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unclear from subgroup analysis paper but full TRIPICU paper states block randomisation ( <a href="#">Lacroix 2007</a> ): randomisation was centralised with assignment data posted on the Internet. Patients were assigned to study groups in blocks of 2 or 4 that were randomly distributed and stratified according to centre and 3 age groups (< 28 days, 29-364 days, and > 364 days)

Allocation concealment (selection bias)	Low risk	Unclear from subgroup analysis paper but full TRIPICU paper states block randomisation (Lacroix 2007): randomisation was centralised with assignment data posted on the Internet. Patients were assigned to study groups in blocks of 2 or 4 that were randomly distributed and stratified according to centre and 3 age groups (< 28 days, 29-364 days, and > 364 days)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Clinicians and carers were reported as being not blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The statistician and members of the data and safety monitoring committee were reported as being blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were included in the analysis. No patients were lost to follow-up A per-protocol analysis was performed on the primary outcome data excluding from the analysis 10 patients who did not meet their pre-defined criteria for good adherence (= 80%), 1 wrongly included patient who was younger than 28 days and 4 patients who could not be categorised according to the Risk Adjustment for Congenital Heart Surgery (RACHS-1) method. The trials reported that the results of this per-protocol analysis differed slightly from the ITT analysis (where all trial patients were included). As per this review's protocol, the ITT data have been used in the analysis of the primary outcome for this trial
Selective reporting (reporting bias)	Low risk	All outcomes identified in the methods were accounted for in results section of the trial report
Other bias	Low risk	None reported

Methods	Type of study: parallel RCT Type of publication: full Setting: Children's Hospital, Hangzhou, China Number of centres: 1 Dates (start and end): October 2010 to April 2011 Follow-up: not stated Number of patients randomised: 217 in the cell saver group, 92 in the control group Number of patients analysed (primary outcome): 217 in the cell saver group, 92 in the control group	
Participants	Inclusion: Chinese paediatric patients undergoing open heart operations with CPB Age: cell salvage: median 1.167 years (IQR 0.637 to 3.833), mean 2.55 years (SD 2.55) ; control: median 1.250 years (IQR 0.555 to 2.479), mean 2.05 years (SD 2.27) Weight: cell salvage: mean 11.09 kg (SD 6.48); control: mean 10.03 kg (SD 4.973) Gender (M/F): cell salvage: 108/109; control group: 42/50 Exclusion: not reported	
Interventions	2 groups: cell salvage and control Intervention arm: cell salvage group: the residual CPB circuit blood was re-infused after the cell saving procedure Comparator arm: control group: patients were directly transfused with allogenic red cells after their operation and the residual CPB circuit blood was discarded. Red cells added to circuit prime during CPB and in ICU postoperatively	
Outcomes	Primary: <ul style="list-style-type: none"><li>• postoperative clinical outcome</li></ul> Other outcomes: <ul style="list-style-type: none"><li>• allogenic red cell requirements</li><li>• haematocrit on the first day in ICU</li><li>• postoperative chest tube drainage</li><li>• intrahospital mortality</li><li>• respiratory morbidity</li><li>• renal dysfunction</li></ul>	
Notes	Funding: supported by the National Science and Technology Foundation of China (2102BA105B05), the Zhejiang Province innovation team for the early screening and intervention of birth defects (2010R50045), the Health Bureau of Zhejiang Provincial Key Program (2012ZDA030; 2012ZDA031), and the Fundamental Research Funds for the Central Universities, Ministry of Education (2011KYJD008; 2012QNA7041) Sample size: although the patients were randomly divided into 2 groups, the numbers of patients in the 2 groups were not equal. This was because in the early stage of the study, they only had one cell-saver machine. Later, they bought a second machine, which ultimately led to a significant difference in the numbers of patients in the 2 arms of the trial	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	No information was provided to enable an assessment of random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information was provided to enable an assessment of adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported so insufficient information to make definite judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in the analysis of outcome data and no patients were lost during follow-up
Selective reporting (reporting bias)	Unclear risk	The trial did not define the outcomes they were interested in; therefore, there is insufficient information to identify whether there was reporting bias in these trials
Other bias	Unclear risk	None reported. It would be difficult to rule out as very little methodological detail was provided in the trial report

CATS: continuous autotransfusion system; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; FDA: Food and Drug Administration (US); Hb: haemoglobin; ICU: intensive care unit; IL: interleukin; IQR: interquartile range; ITT: intention to treat; MODS: multiple organ dysfunction syndrome; PaO<sub>2</sub>: partial oxygen pressure of the arterial blood; PCICU: paediatric cardiac intensive care unit; P<sub>p</sub>: pulmonary arterial pressure; P<sub>p</sub>/P<sub>s</sub>: pulmonary to systemic arterial pressure ratio; P<sub>s</sub>: systemic arterial pressure; RCT: randomised controlled trial; rSO<sub>2</sub>: regional cerebral oxygen saturation; SD: standard deviation; SEM: standard error of the mean; TRIPICU: Transfusion Requirements in Pediatric Intensive Care Units; URM: University of Rochester Medical Center.

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

Study	Reason for exclusion
Blackwood 2010	Ineligible type of study: cohort study (full paper had to be obtained to assess eligibility)
Chicella 2003	Ineligible intervention: screening reference did not contain full abstract so eligibility could not be assessed without full details

(Continued)

Cholette 2013	Ineligible intervention: no definite allogeneic blood transfusion intervention arm. The primary intervention in the trial was cell salvage blood and the control arm received crystalloid/albumin with or without red cell transfusion if anaemic. It is likely that a significant proportion of the control arm would not have received an allogeneic red cell transfusion. The intervention of cell salvage could be examined in a future review
Dietrich 2005	Ineligible type of study: observational study and retrospective analysis (abstract had to be obtained to assess eligibility)
Embil 1968	Ineligible type of study: not an RCT, rather a prospective single-arm study (full paper had to be obtained to assess eligibility)
Fergusson 2009	Ineligible patient group: based on a general neonatal population and not specifically in neonates with congenital heart disease undergoing cardiac surgery
Germann 1998	Ineligible type of study: review of evidence base to 1998 (further details had to be obtained to assess eligibility)
Gruenwald 2008	Ineligible intervention: reconstituted fresh whole blood compared with standard blood component therapy
Gupta 2007	Ineligible patient group: patients with congenital heart disease (patent ductus arteriosus) did not undergo cardiac surgery
Hertfelder 1992	Ineligible type of study: not an RCT, rather a single-arm comparison of whole blood versus blood component therapy in paediatric open-heart surgery
Kaltmann 2010	Ineligible type of study: a commentary not an RCT (further details obtained to assess eligibility)
Kipps 2011	Ineligible type of study: data taken from 2 related studies to explore and analyse the duration of mechanical ventilation in infants undergoing reparative cardiac surgery
Manno 1991	Ineligible intervention: red cells were not an independent intervention as very fresh whole blood was compared with older whole blood and then compared with red blood cells, platelets and fresh frozen plasma
McEwan 2007	Ineligible type of study: review article (full paper obtained to assess eligibility)
Moritz 2000	Ineligible intervention: red cell data not presented independently of other blood products used. Blood components (packed red cells, fresh frozen plasma and platelets) were compared with fresh whole blood
Mou 2004	Ineligible intervention: the reconstituted blood (0.5 units of packed red cells) was mixed with 0.5 units of fresh frozen plasma to achieve a haematocrit of 25%. Reconstituted blood was then compared with fresh whole blood so red cell data were not presented independently of the other blood products used
Newburger 2008	Ineligible intervention: haematocrit values (25% versus 35%) were compared

RCT: randomised controlled trial.

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

### Cholette 2010a

Methods	Interventional study Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Inclusion criteria: 1. weight $\leq$ 20 kg 2. cardiac surgery with CPB at URMC 3. informed consent
Interventions	Patients will be randomly assigned to 1 of 2 groups: 1. conventional transfusion: active comparator infants will receive packed red blood cells, crystalloid and colloid for haemodynamic instability per the usual routine at the discretion of the attending intensive care physician. 2. cell saver: experimental infants will receive washed cell-saver red blood cells for haemodynamic instability in the first 24-hour postoperative period as long as Hg < 13 g/dL and cell-saver is available
Outcomes	Primary: <ul style="list-style-type: none"> <li>comparison of volume of allogeneic blood products and crystalloid/colloid infusions between groups patients randomised to receive washed intraoperative cell salvage versus our current standard for volume replacement for the first 24 hours post operatively</li> </ul> Secondary: <ul style="list-style-type: none"> <li>comparison of bleeding, use of coagulant products and inflammatory markers between groups by comparing measures of bleeding (mediastinal chest tube drainage, haemoglobin, platelet counts), the use of coagulant products (fresh frozen plasma, platelets, cryoprecipitate) and inflammatory/immunomodulatory markers (CRP and IL-6/IL-10 ratio) between patients randomised to receive washed intraoperative cell salvage versus our current standard of care for volume replacement</li> <li>comparison of clinical outcomes between groups by comparing clinical outcome measures (ventilator days, PCICU duration, thrombosis, bacterial infections and mortality) between patients randomised to receive washed intraoperative cell salvage versus our current standard of care for volume replacement</li> </ul>
Notes	We will need to be able to compare packed red blood cell with cell saver red blood cell to include in this systematic review Trial reference number: NCT0121366

### Hajjar 2010

Methods	Interventional study Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	512 patients undergoing cardiac surgery

Interventions	Patients were randomised into 2 groups: 1. liberal strategy of transfusion to maintain a haematocrit at least at 30% 2. restrictive strategy of transfusion to maintain a haematocrit at least at 24%
Outcomes	Primary: <ul style="list-style-type: none"> <li>• composite endpoint of 30-day all-cause mortality or severe morbidity</li> </ul> Secondary: <ul style="list-style-type: none"> <li>• rates of complications</li> <li>• haemoglobin concentrations</li> <li>• number of patients receiving a red cell transfusion</li> <li>• number of transfused red cell units</li> </ul>
Notes	A short abstract is all that is available in English of this doctoral thesis from Dr Hajjar (University of Sao Paulo, Brazil). Email contact has been made with Dr Hajjar through one of the authors of this review (RG). We are awaiting a response to this email. If we were able to have access to the full thesis and the thesis is available in English, we will include this trial in full in the review

CPB: cardiopulmonary bypass; CRP: C-reactive protein; IL: interleukin; PCICU: paediatric cardiac intensive care unit; URM: University of Rochester Medical Center.

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

### Chollette 2012a

Trial name or title	Prospective Randomised Controlled Clinical Trial Comparing a Restrictive Versus Liberal Transfusion Protocol in Neonates and Infants Undergoing Surgery for Congenital Heart Disease
Methods	Single centre RCT
Participants	Children $\leq 6$ months of age with congenital cardiac disease undergoing cardiac surgery with cardiopulmonary bypass Exclusions are presence of a known bleeding disorder or coagulopathy; age $> 6$ months or lack of informed consent
Interventions	Restrictive red cell transfusion strategy: red blood cells will be transfused if the Hb level falls below 7.0 g/dL for biventricular repairs and $< 9.0$ g/dL for single ventricle palliations Liberal red cell transfusion strategy: red blood cells will be transfused for Hb $< 9.5$ g/dL for biventricular repairs and $< 12.0$ g/dL for single ventricle palliations
Outcomes	Primary <ul style="list-style-type: none"> <li>• oxygen utilisation derived from the arterio-venous oxygen difference</li> </ul> Arterial and venous oxygen saturations will be measured every 4 hours for 48-72 hours and will be used to calculate arterio-venous oxygen content differences Secondary <ul style="list-style-type: none"> <li>• volume of red cell transfused</li> </ul> The total numbers of red cell transfusions given during the immediate postoperative period (first 7 days) will

**Cholette 2012a** (Continued)

	be compared between groups
Starting date	January 2012
Contact information	Jill.Cholette@urmc.rochester.edu
Notes	Due to complete: August 2013. ClinicalTrials.gov ID Number: NCT01484886

**Reeves 2008**

Trial name or title	A Multi-Centre Randomised Controlled Trial of Transfusion Indication Threshold Reduction (TITRe 2) Study on Transfusion Rates, Morbidity and Healthcare Resource Use Following Cardiac Surgery
Methods	Multicentred RCT
Participants	Adults of either sex, aged $\geq 16$ years undergoing cardiac surgery (defined as coronary artery bypass grafting, valvular or aortic surgery or surgical correction of congenital cardiac disease) who have a postoperative Hb level $< 9.0$ g/dL or haematocrit $< 27\%$ at any stage during patient's postoperative hospital stay (i.e. on PCICU or cardiac surgical ward). They must be able to give written informed consent
Interventions	<p>If the patient's Hb falls below 9.0 g/dL they will then become eligible for the main study and will be randomised between:</p> <ul style="list-style-type: none"> <li>• liberal (control) group (eligible for transfusion when Hb <math>&lt; 9.0</math> g/dL)</li> <li>• restrictive (experimental) group (continue monitoring Hb level. Eligible for transfusion if Hb <math>&lt; 7.5</math> g/dL)</li> </ul> <p>In both groups, 1 unit of red blood cells should be administered and the Hb level checked before transfusing another unit</p>
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>• binary composite outcome of any serious infectious or ischaemic events in the first 3 months after randomisation</li> </ul> <p>Secondary:</p> <p>Data will be collected to characterise the following secondary outcomes at 3 months (unless otherwise stated) :</p> <ul style="list-style-type: none"> <li>• units of red blood cell and other blood components transfused during a patient's hospital stay</li> <li>• proportion of patients experiencing an infectious event</li> <li>• proportion of patients experiencing an ischaemic event</li> <li>• quality of life (using EUROQoL EQ5D)</li> <li>• length of ICU and HDU stay</li> <li>• length of hospital stay</li> <li>• all-cause mortality</li> <li>• cumulative resource use, cost and cost-effectiveness</li> </ul>
Starting date	August 2009
Contact information	Contact: TITRe 2 Trial, CTEU, Level 7, Queen's Building, Bristol Royal Infirmary, Upper Maudlin Street, Bristol, BS2 8HW



	Telephone: 0117 342 3564 Email: titre2-trial@bristol.ac.uk
Notes	Study closed: March 2013 and the data is being cleaned ahead of analysis later in 2013 To be included in this review, the trial will need to analyse the congenital cardiac disease group as an independent subgroup Trial reference number: HTA 06/402/94

# Steiner 2010

Trial name or title	Addressing the Question of the Effect of Red Blood Cell Storage on Clinical Outcomes: The Red Cell Storage Duration Study (RECESS)
Methods	Multicentre, partially blinded, RCT
Participants	<ol style="list-style-type: none"> <li>1. <math>\geq 12</math> years old</li> <li>2. <math>\geq 40</math> kg body weight</li> <li>3. Scheduled complex cardiac surgery with planned use of median sternotomy</li> <li>4. Patients <math>\geq 18</math> years must have a Transfusion Risk Understanding Scoring Tool (TRUST) probability score <math>\geq 3</math></li> </ol>
Interventions	Study participants are randomised by the blood bank co-ordinators to receive red blood cells stored for either $\leq 10$ days ('fresh') or $\geq 21$ days ('old'). If a patient does not receive any red cell transfusions between randomisation and 96 hours following the end of the surgery, the patient will be withdrawn from the study. Patients who do receive red cell transfusions during this time period are transfused according to their randomised treatment arm up to 28 days after surgery, until hospital discharge or death, whichever occurs first
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>• change in clinical outcome assessed using the Multiple Organ Dysfunction Score (MODS), which is a composite endpoint of multisystem organ dysfunction</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>• all-cause mortality through 28 days</li> <li>• change in MODS through postoperative day 28, hospital discharge, or death, whichever comes first</li> <li>• composite of major in-hospital postoperative complications through postoperative day 7, hospital discharge or death, whichever occurs first (death, stroke, myocardial infarction, renal failure or culture-confirmed sepsis/septic shock) <ul style="list-style-type: none"> <li>• composite of major cardiac events through postoperative day 7, hospital discharge or death, whichever occurs first (death, myocardial infarction, low cardiac output, ventricular tachycardia or ventricular fibrillation)</li> <li>• composite of major pulmonary events through postoperative day 7, hospital discharge or death, whichever occurs first (pulmonary embolism or any mechanical ventilation more than 48 hours after surgery) <ul style="list-style-type: none"> <li>• ventilation duration through postoperative day 28, hospital discharge or death, whichever comes first</li> <li>• any mechanical ventilation from 48 hours postoperative to day 28, hospital discharge or death, whichever occurs first</li> </ul> </li> <li>• changes in the following laboratory parameters, from the preoperative baseline to the worst recorded postoperative value through to postoperative day 7, hospital discharge or death, whichever occurs first <ul style="list-style-type: none"> <li>• serum creatinine</li> <li>• troponin-I</li> </ul> </li> </ul> </li> </ul>

**Steiner 2010** (Continued)

	<ul style="list-style-type: none"> <li>• lactate</li> <li>• liver function tests (bilirubin, and for children also alanine aminotransferase)</li> <li>• days to first bowel movement through postoperative day 28, hospital discharge or death, whichever comes first</li> <li>• days to first solid food through postoperative day 28, hospital discharge or death, whichever comes first</li> </ul>
Starting date	January 2010
Contact information	Corresponding author: C.P. Stowell. Address: Blood Transfusion Service, GRJ 148, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA Telephone: +1 617 726 2815; fax: +1 617 726 6832 Email address: cstowell@partners.org (C.P. Stowell)
Notes	Due to complete: October 2013 The trial would need to present results for patients undergoing cardiac surgery for congenital cardiac disease as a separate group to be included in this systematic review

Hb: haemoglobin; HDU: high dependency unit; ICU: intensive care unit; PCICU: paediatric cardiac intensive care unit; RCT: randomised controlled trial.

## DATA AND ANALYSES

### Comparison 1. Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality: short term (30 days post surgery)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Standard/non-standard cardiopulmonary bypass	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause mortality: long term - at 2 years	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Severe adverse events: cardiac events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Severe adverse events: acute lung injury	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Severe adverse event: thromboembolism	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Standard/non-standard cardiopulmonary bypass prime	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Severe adverse events: renal failure (needing renal replacement therapy)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Severe adverse events: infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Severe adverse events: haemorrhage (return to theatre for bleeding)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Transfusion trigger	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Standard/non-standard cardiopulmonary bypass	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

9 Haematocrit (%) / haemoglobin (g/dL) levels postoperatively	5	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Transfusion trigger - haemoglobin (g/dL)	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Standard/non-standard cardiopulmonary bypass prime - haematocrit (%)	3	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Volume or number of red cell units transfused	4	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Transfusion trigger	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Leukocyte depletion	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Standard/non-standard cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Number of participants receiving fresh frozen plasma	2	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Transfusion trigger	2	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Number of participants receiving a platelet transfusion	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Transfusion trigger	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Volume or number of other blood products transfused: platelets	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Standard/non-standard cardiopulmonary bypass prime	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Volume or number of other blood products transfused: cryoprecipitate	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Standard/non-standard cardiopulmonary bypass prime	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Volume or number of other blood products transfused: fresh frozen plasma	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Standard/non-standard cardiopulmonary bypass prime	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Postoperative chest drain output	3	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Transfusion trigger	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Standard/non-standard cardiopulmonary bypass	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Duration of mechanical ventilation	2	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Transfusion trigger - after randomisation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Transfusion trigger - total paediatric intensive care unit stay	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Leukocyte depletion	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Duration of intensive care unit stay	5	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Transfusion trigger	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Leukocyte depletion	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

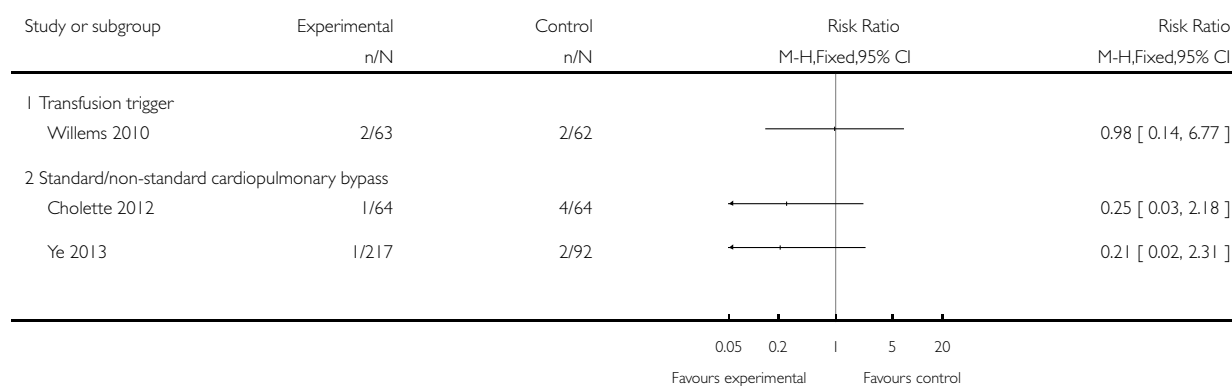
18.3 Standard/non-standard cardiopulmonary bypass prime	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Lactate Levels (mmol/L)	4	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 At baseline	3	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Cardiopulmonary bypass circuit prime after line connection and 5 minute re-circulation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 10 minutes after the start of cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.4 'Peak' as defined by the study	2	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.5 At 28°C during re-warming	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.6 Immediately after cardiopulmonary bypass and clamp of arterial cannula	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Sodium (Na <sup>+</sup> ) levels (mmol/L)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 At baseline	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Cardiopulmonary bypass circuit prime after line connection and 5 minute re-circulation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 At 36°C after re-warming	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.4 Immediately after cardiopulmonary bypass and clamp of arterial cannula	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Potassium (K <sup>+</sup> ) levels (mmol/L)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Cardiopulmonary bypass circuit prime after line connection and 5 minute re-circulation	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 At 28°C during re-warming	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Immediately after cardiopulmonary bypass and clamp of arterial cannula	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Blood glucose (mg/dL)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 After induction	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Prior to cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.3 In the bypass priming solution prior to initiation of cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.4 10 minutes after initiation of cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.5 Prior to separation from cardiopulmonary bypass	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.6 After administration of protamine	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

### Analysis 1.1. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 1 All-cause mortality: short term (30 days post surgery).

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 1 All-cause mortality: short term (30 days post surgery)

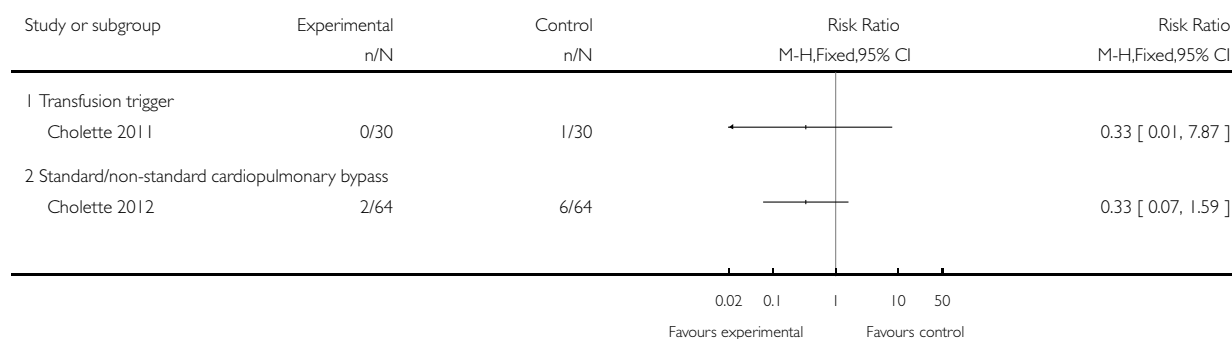


### Analysis 1.2. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 2 All-cause mortality: long term - at 2 years.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 2 All-cause mortality: long term - at 2 years

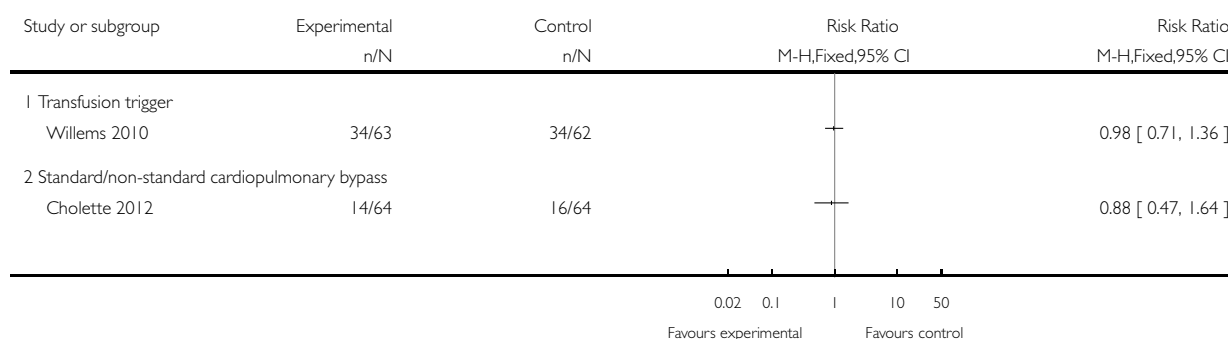


### Analysis 1.3. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 3 Severe adverse events: cardiac events.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 3 Severe adverse events: cardiac events

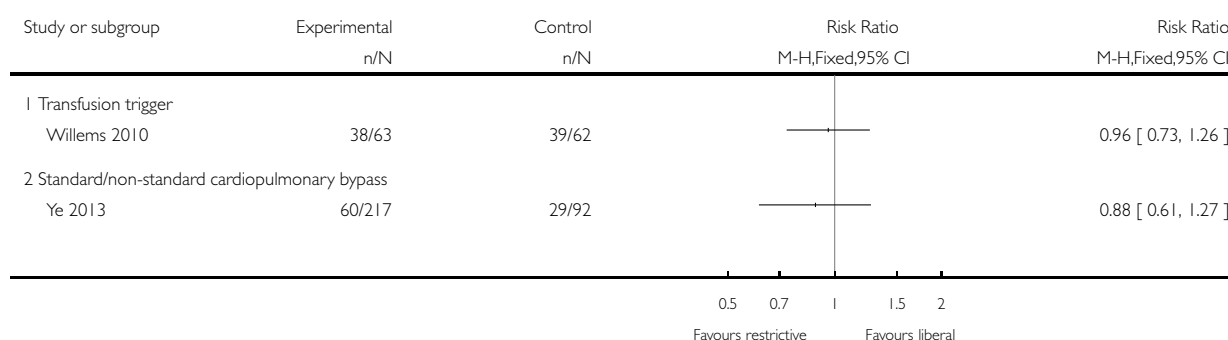


### Analysis 1.4. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 4 Severe adverse events: acute lung injury.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 4 Severe adverse events: acute lung injury

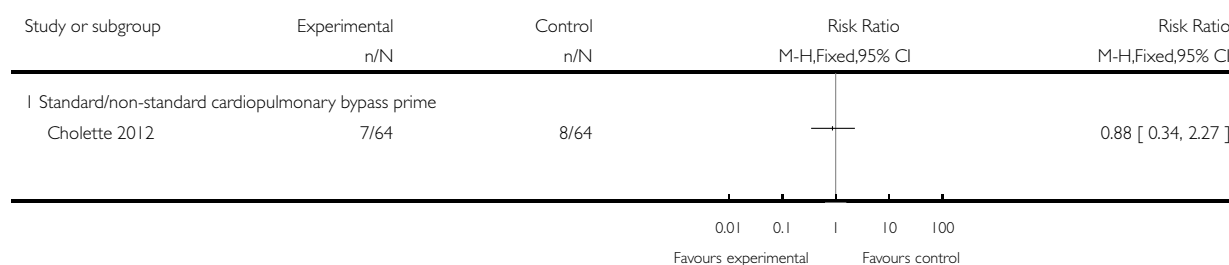


### Analysis 1.5. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 5 Severe adverse event: thromboembolism.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 5 Severe adverse event: thromboembolism

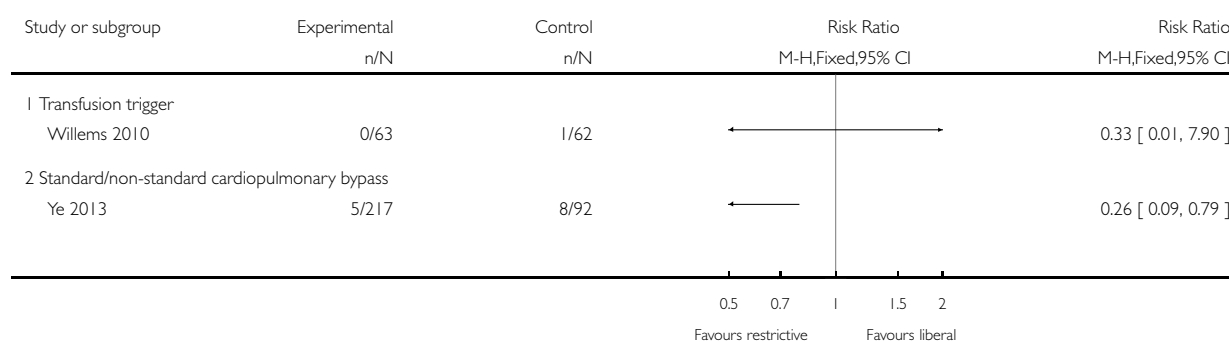


### Analysis 1.6. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 6 Severe adverse events: renal failure (needing renal replacement therapy).

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 6 Severe adverse events: renal failure (needing renal replacement therapy)



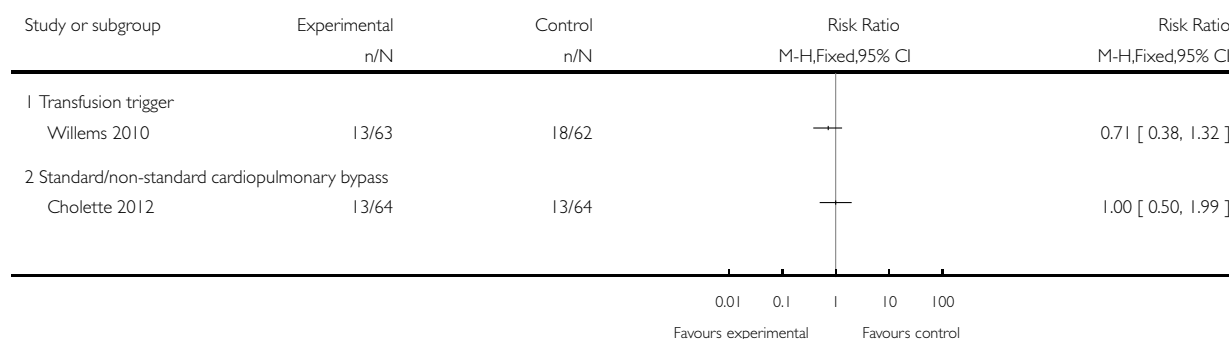


### Analysis 1.7. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 7 Severe adverse events: infection.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 7 Severe adverse events: infection

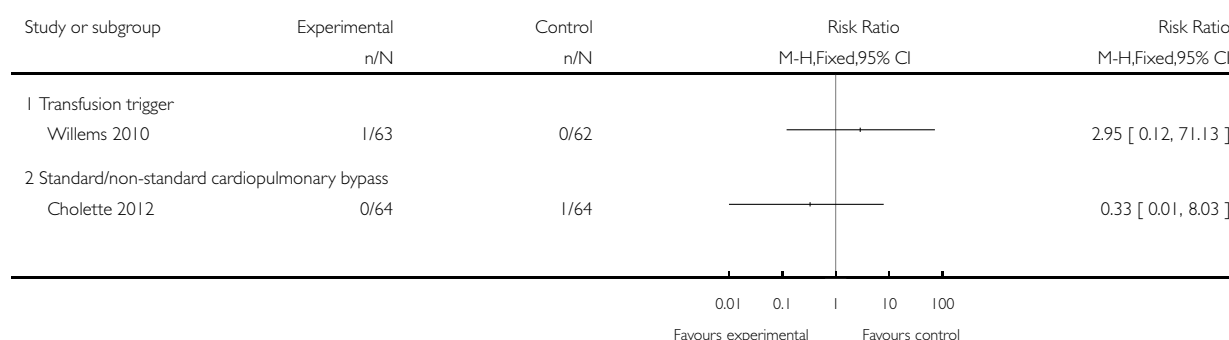


### Analysis 1.8. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 8 Severe adverse events: haemorrhage (return to theatre for bleeding).

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 8 Severe adverse events: haemorrhage (return to theatre for bleeding)

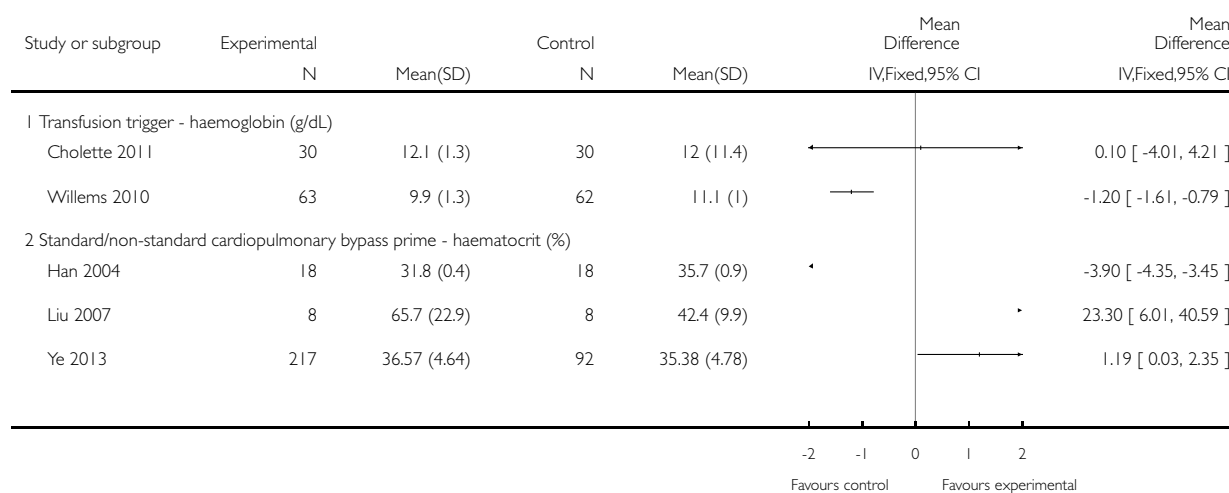


# **Analysis 1.9. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 9 Haematocrit (%)/haemoglobin (g/dL) levels postoperatively.**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 9 Haematocrit (%)/haemoglobin (g/dL) levels postoperatively

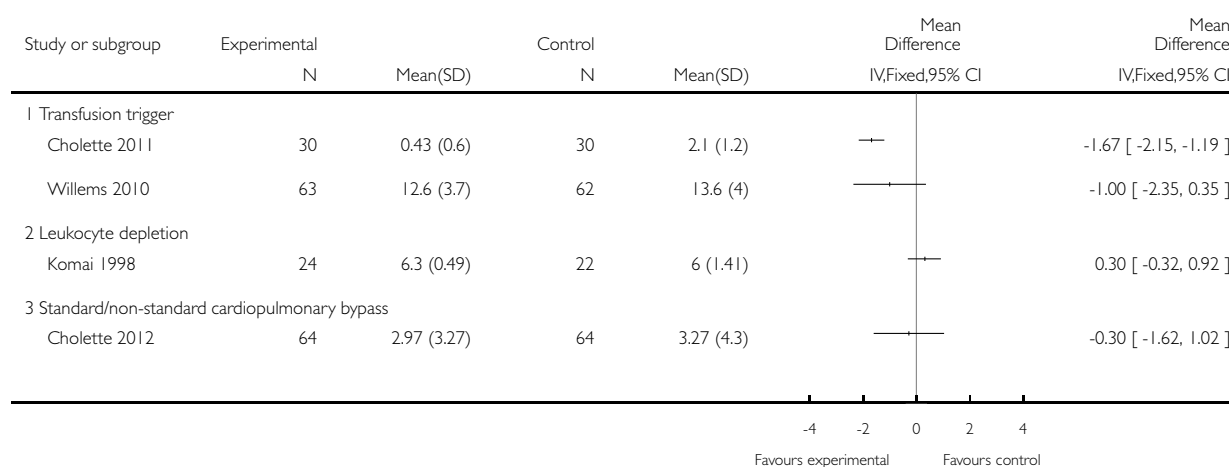


### Analysis 1.10. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 10 Volume or number of red cell units transfused.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 10 Volume or number of red cell units transfused

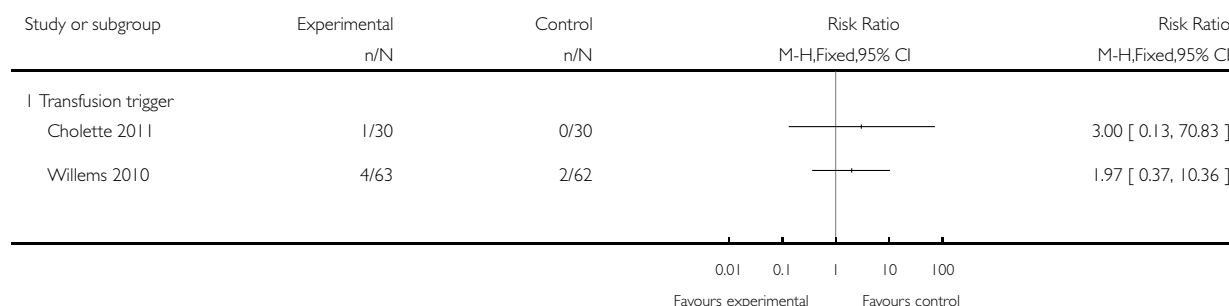


### Analysis 1.11. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 11 Number of participants receiving fresh frozen plasma.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 11 Number of participants receiving fresh frozen plasma

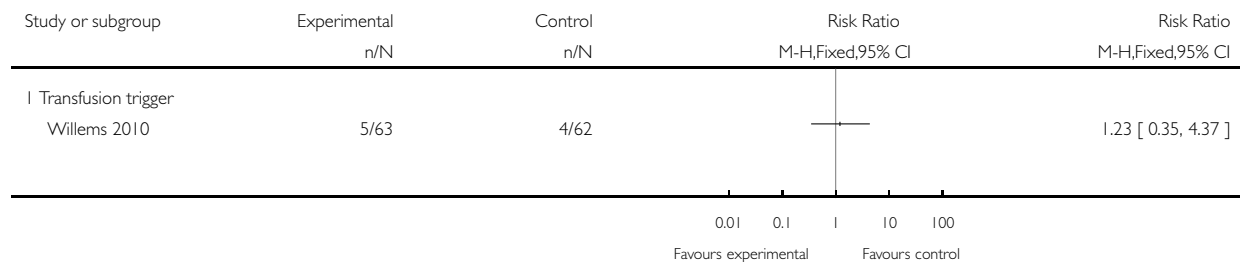


### Analysis 1.12. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 12 Number of participants receiving a platelet transfusion.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 12 Number of participants receiving a platelet transfusion



### Analysis 1.13. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 13 Volume or number of other blood products transfused: platelets.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 13 Volume or number of other blood products transfused: platelets

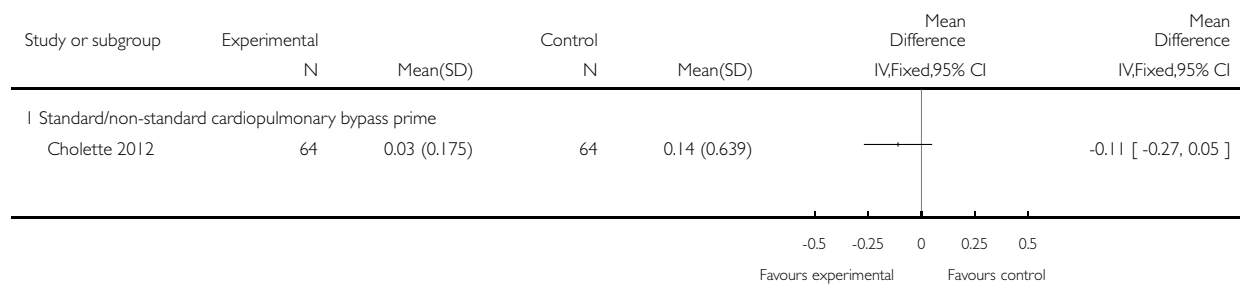


**Analysis 1.14. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 14 Volume or number of other blood products transfused: cryoprecipitate.**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 14 Volume or number of other blood products transfused: cryoprecipitate

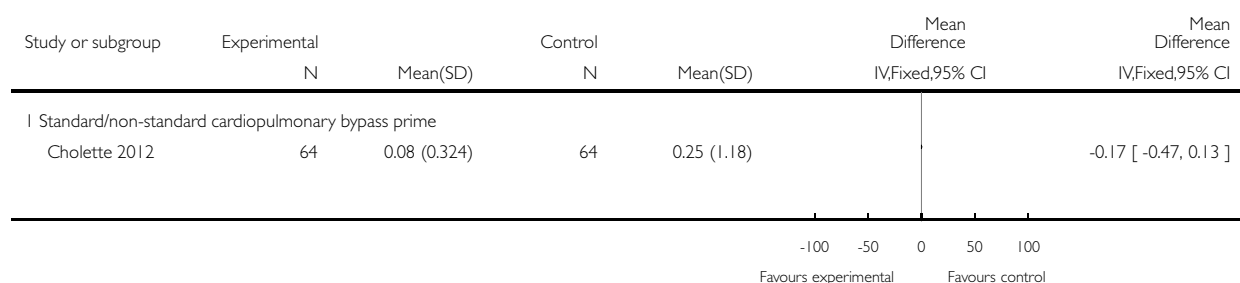


**Analysis 1.15. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 15 Volume or number of other blood products transfused: fresh frozen plasma.**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 15 Volume or number of other blood products transfused: fresh frozen plasma

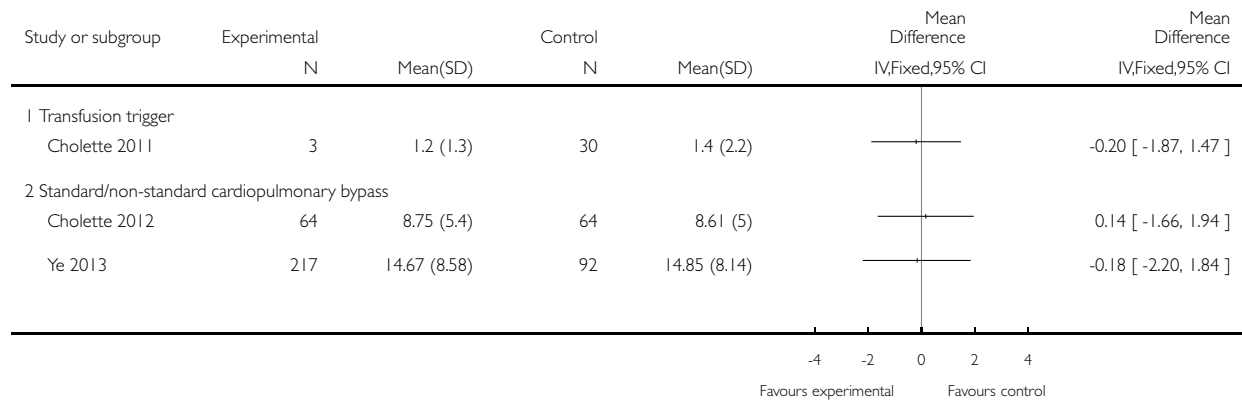


# **Analysis 1.16. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 16 Postoperative chest drain output.**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 16 Postoperative chest drain output

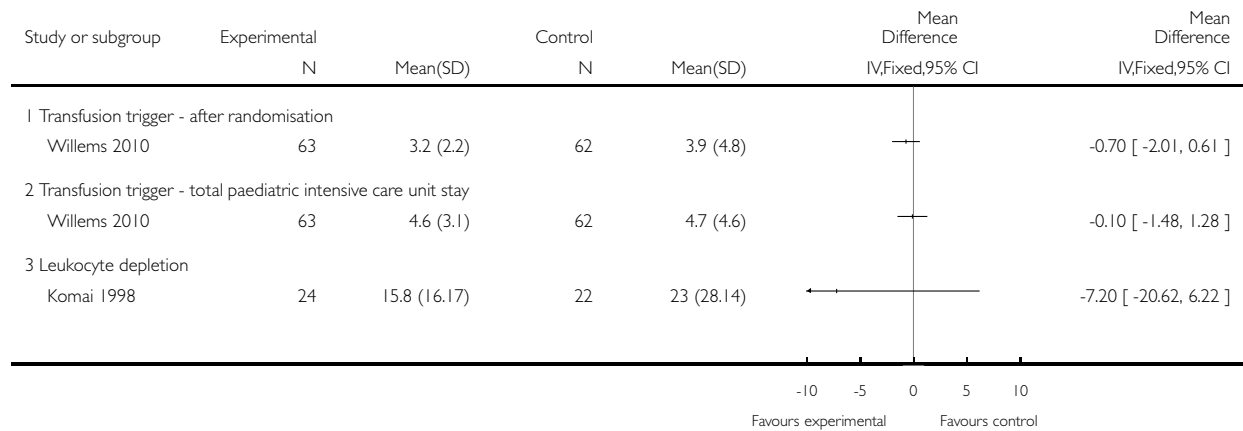


### Analysis 1.17. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 17 Duration of mechanical ventilation.

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 17 Duration of mechanical ventilation

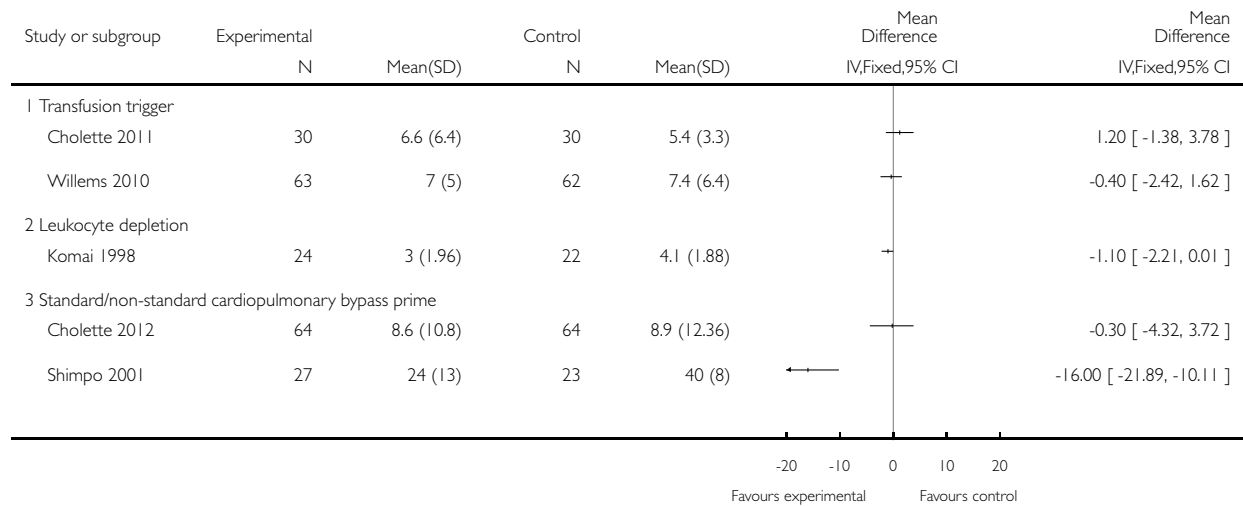


# **Analysis 1.18. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 18 Duration of intensive care unit stay.**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 18 Duration of intensive care unit stay



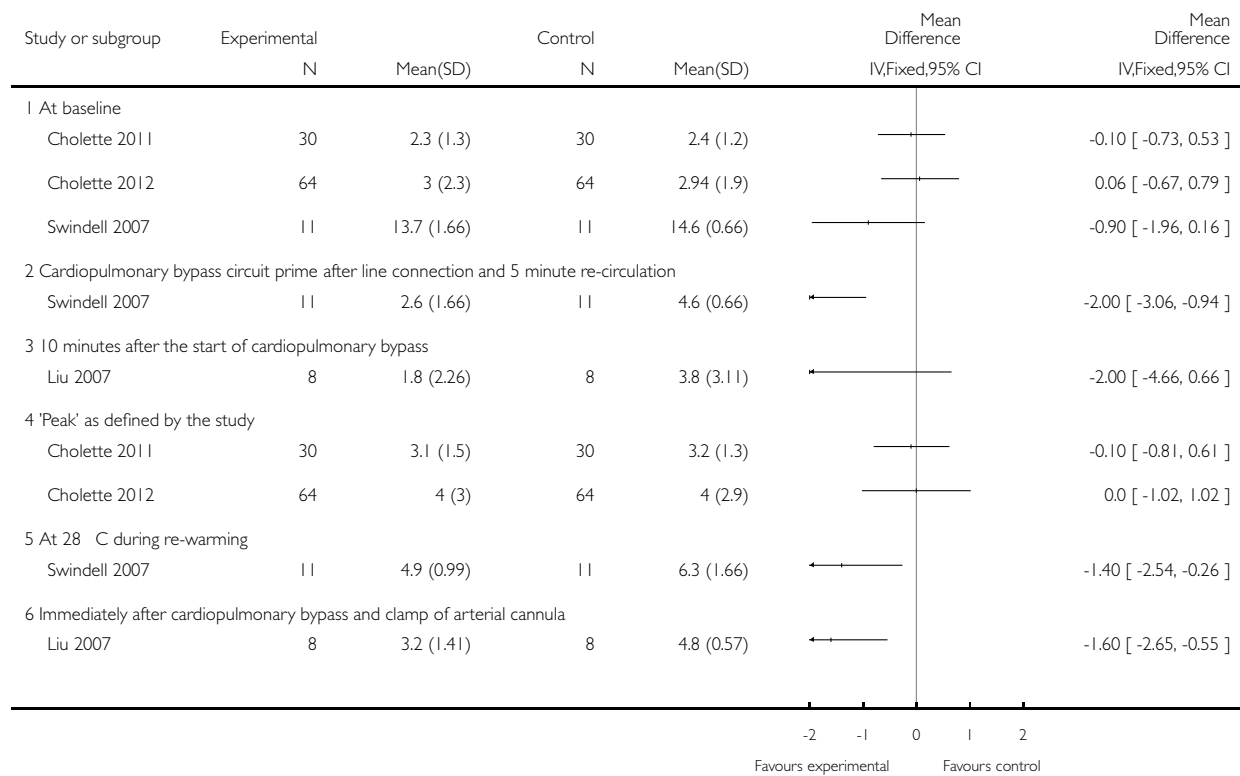


### Analysis 1.19. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 19 Lactate Levels (mmol/L).

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 19 Lactate Levels (mmol/L)

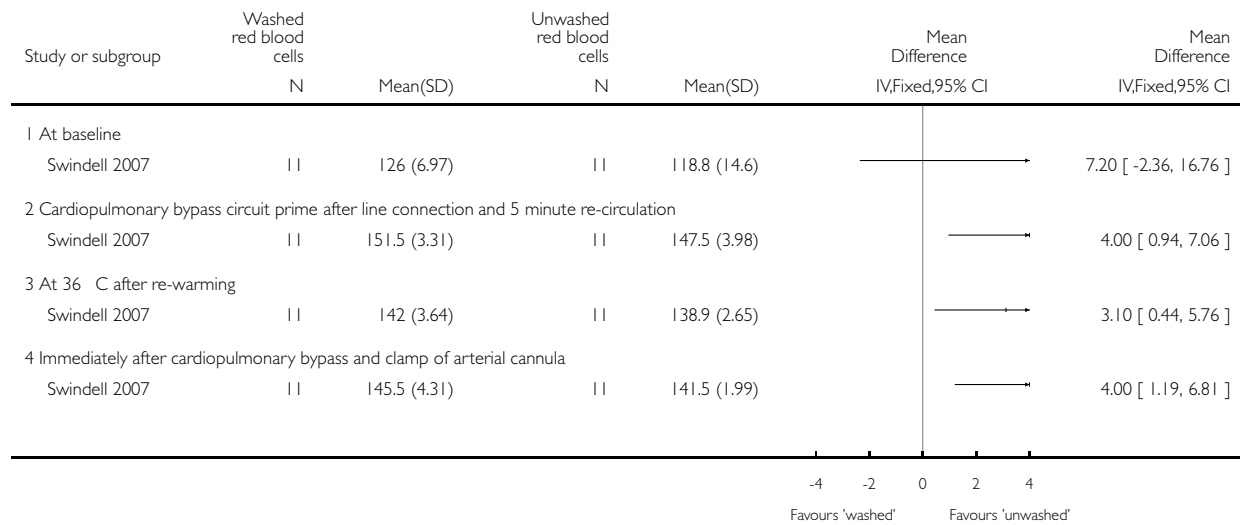


**Analysis 1.20. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 20 Sodium (Na<sup>+</sup>) levels (mmol/L).**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 20 Sodium (Na<sup>+</sup>) levels (mmol/L)

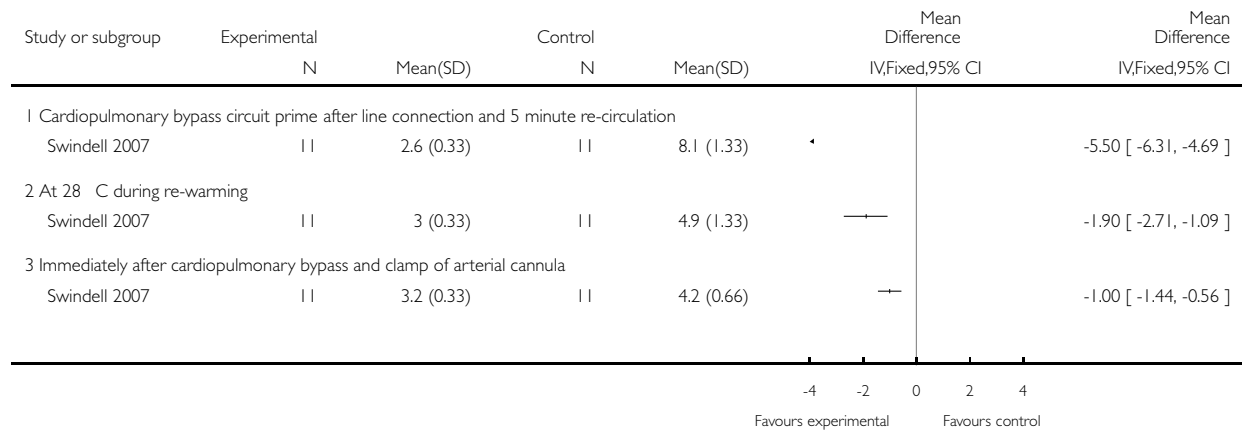


# **Analysis 1.21. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 21 Potassium (K<sup>+</sup>) levels (mmol/L).**

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 21 Potassium (K<sup>+</sup>) levels (mmol/L)

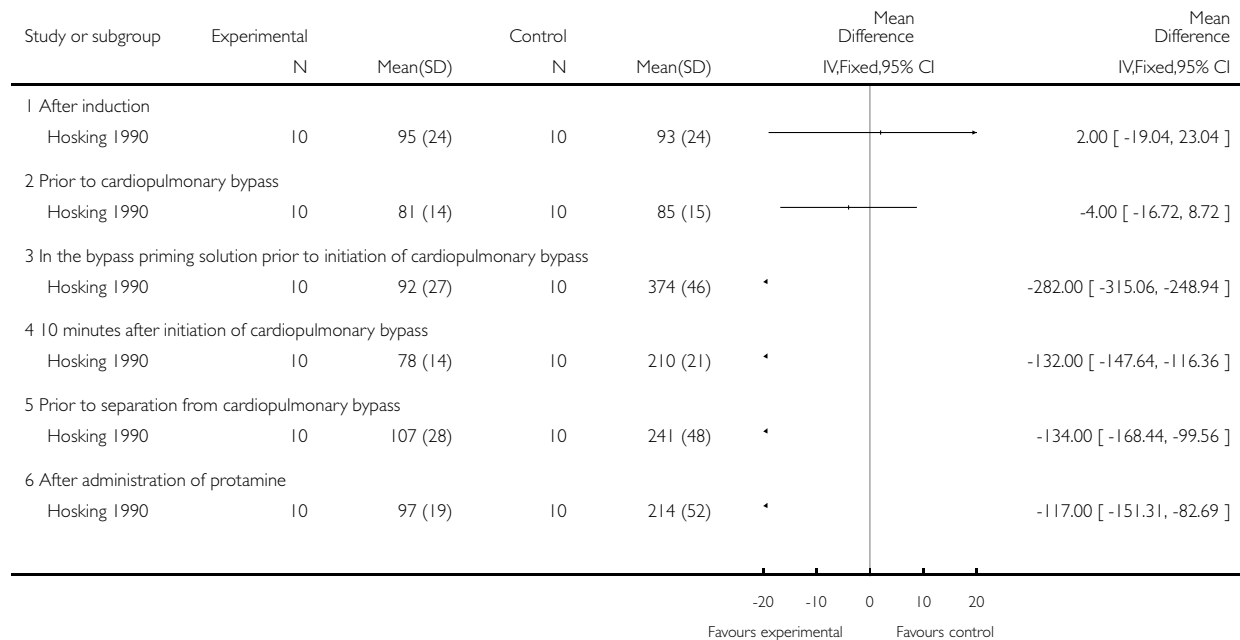


## Analysis 1.22. Comparison 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease, Outcome 22 Blood glucose (mg/dL).

Review: Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease

Comparison: 1 Comparisons of red cell transfusion at the time of cardiac surgery in people with congenital heart disease

Outcome: 22 Blood glucose (mg/dL)



## ADDITIONAL TABLES

**Table 1. Haematocrit levels (%) postoperatively**

	Intervention	Comparator
Ye 2013* (standard/non-standard CPB prime: cell salvage versus no cell salvage)	36.2 (33.6 to 39.6)	34.8 (33.0 to 37.57)

\*This outcome is reported as median values (with 25 and 75 percentiles).

CPB: cardiopulmonary bypass.

**Table 2. Chest tube drainage**

	Intervention	Comparator
<a href="#">Ye 2013</a> * (standard/non-standard CPB prime: cell salvage versus no cell salvage)	12.67 mL/kg (9.3875 to 17.43)	13.57 mL/kg (8.7300 to 18.45)

\*This outcome is reported as median values (with 25 and 75 percentiles).  
CPB: cardiopulmonary bypass.

**Table 3. Duration of mechanical ventilation**

	Intervention	Comparator
<a href="#">Cholette 2011</a> ** (transfusion trigger: restrictive versus liberal red cell transfusion)	23 hours (5 to 625)	20 hours (4 to 216)
<a href="#">Willems 2010</a> (transfusion trigger: restrictive versus liberal red cell transfusion)	4.6 hours (SD 3.1)	4.7 hours (SD 4.6)
<a href="#">Komai 1998</a> * (leukoreduced red cell versus non-leukoreduced red cell transfusion)	15.8 hours (16.17)	23.0 hours (28.14)
<a href="#">de Vries 2004</a> ** (leukoreduced red cell versus non-leukoreduced red cell transfusion)	19 (9 to 48) hours	21 hours (16 to 54)
<a href="#">Cholette 2012</a> ** (standard/non-standard CPB prime: washed versus un washed red blood cells)	45 hours (4 to 1008)	51.5 hours (3 to 1200)
<a href="#">Shimpo 2001</a> (standard/non-standard CPB prime: ultrafiltration versus no ultrafiltration)	Exact figures not given but manuscript reports that the ultrafiltration arm had a significantly shorter duration of mechanical ventilation than the no ultrafiltration arm	Exact figures not given but manuscript reports that the ultrafiltration arm had a significantly shorter duration of mechanical ventilation than the no ultrafiltration arm
<a href="#">Ye 2013</a> ** (standard/non-standard CPB prime: cell salvage versus no cell salvage)	7.16 hours (4.5 to 24.5)	6.83 hours (4.69 to 25)

\*This outcome is reported as mean (SD), where the SD has been calculated by the review authors from the standard error of the mean values reported by the study.

\*\*This outcome is reported as median values (with 25 and 75 percentiles).  
CPB: cardiopulmonary bypass; SD: standard deviation.

**Table 4. Duration of intensive care unit stay**

	Intervention	Comparator
<a href="#">de Vries 2004*</a> (leukoreduced red cell versus non-leukoreduced red cell transfusion)	1 day (1 to 3.7)	1 day (1 to 5)
<a href="#">Shimpo 2001</a> (standard/non-standard CPB prime: ultrafiltration versus no ultrafiltration)	mean 24 hours (SD 13)	mean 40 hours (SD 8)

\*This outcome is reported as median values (with 25 and 75 percentiles).

CPB: cardiopulmonary bypass; SD: standard deviation.

**Table 5. Included studies by intervention and age groups**

	Cyanosis	Neonates	Neonates/paediatric	Paediatric	Adults
Re-strictive transfusion trigger versus liberal transfusion trigger	Acyanotic	None	None	<a href="#">Willems 2010</a>	None
	Cyanotic	None	None	<a href="#">Cholette 2011</a>	None
	Both	None	None	None	None
Volume A red cell transfusion versus volume B red cell transfusion	Acyanotic	None	None	None	None
	Cyanotic	None	None	None	None
	Both	None	None	None	None
Leukoreduced red cell versus non-leukoreduced red cell transfusion	Acyanotic	None	None	<a href="#">Komai 1998</a>	None
	Cyanotic	None	None	None	None
	Both	None	None	<a href="#">de Vries 2004</a>	None
Whole blood versus packed red cell transfusion	Acyanotic	None	None	None	None
	Cyanotic	None	None	None	None
	Both	None	None	None	None
'New' (not near to expiry date) versus 'old' (near to expiry date) red cell transfusion	Acyanotic	None	None	None	None

**Table 5. Included studies by intervention and age groups** (Continued)

	Cyanotic	None	None	None	None
	Both	None	None	None	None
Standard CPB prime versus non-standard CPB prime	Acyanotic	None	None	<a href="#">Han 2004</a> ; <a href="#">Shimpo 2001</a>	None
	Cyanotic	<a href="#">Liu 2007</a>	<a href="#">Swindell 2007</a>	None	None
	Both	None	<a href="#">Cholette 2012</a>	<a href="#">Hosking 1990</a> ; <a href="#">Ye 2013</a>	None

CPB: cardiopulmonary bypass.

**Table 6. Causes of mortality in the included trials**

		Cause of mortality
All-cause mortality: short term (30 days post surgery)	<a href="#">Cholette 2012</a>	Washed group (1 patient) 1 paediatric patient died on POD 0 secondary to a pulmonary hypertensive crisis Unwashed group (4 patients) 1 neonate died in the operating room as a result of diffuse bleeding/coagulopathy 1 neonate died on POD 4 after support was withdrawn as the patient had no LV function and was unable to come off ECMO 1 neonate died on POD 11 following an arrest with acute desaturation, junctional rhythm, poor function on Echo and lactic acidosis 1 neonate died on POD 23 as a result of an arrest stopping breathing and a subsequent inability to resuscitate the patient
	<a href="#">Liu 2007</a>	Not applicable: no deaths reported
	<a href="#">Shimpo 2001</a>	Not applicable: no deaths reported
	<a href="#">Willems 2010</a>	No data on cause of death was reported
	<a href="#">Ye 2013</a>	No data on cause of death was reported
All-cause mortality: long term (at 2 years)	<a href="#">Cholette 2011</a>	1 patient in the liberal transfusion strategy arm died on day 39 from staphylococcal sepsis
	<a href="#">Cholette 2012</a>	Washed group (1 patient) 1 neonate died on POD 57 after care was withdrawn in view of post-operative neurological disease Unwashed group (2 patients) 1 neonate died on POD 61 following an acute arrest and inability to resuscitate the patient 1 6-month-old patient arrested on POD 0 and subsequently arrested

**Table 6. Causes of mortality in the included trials** (Continued)

		and died on POD 90. Autopsy revealed RSV bronchiolitis, acute Ischaemic neuronal necrosis in watershed regions, myocardial necrosis and chronic heart failure
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Echo: echocardiogram; ECMO: extracorporeal membrane oxygenation (machine); LV: left ventricular; POD: postoperative day; RSV: respiratory syncytial virus.

## APPENDICES

### Appendix I. Search strategies

#### Cochrane Central Register of Controlled Trials (CENTRAL)

- #1 MeSH descriptor: [Heart Defects, Congenital] explode all trees
- #2 MeSH descriptor: [Heart Diseases] explode all trees and with qualifiers: [Congenital - CN]
- #3 ((heart\* or cardiac\* or coronary or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular) near/3 (congenital\* or neonat\* or defect\* or abnormal\* or anomal\*))
- #4 (digeorge next (syndrome\* or anomal\* or sequenc\*))
- #5 (transpos\* near/3 (arteries or artery or vessel\*))
- #6 (alagille near/2 syndrome)
- #7 arteriohepatic dysplasia\* or gonadal dysgenesis or subdivided left atrium\* or cardiovertebral syndrome\* or pharyngeal pouch syndrome\* or thymic aplasia syndrome\* or conotruncal anomaly face syndrome
- #8 hepatic hypoplasia or arteriohepatic dysplasia\* or turner\* syndrome or noonan syndrome or arteriohepatic dysplasia\* or bicuspid aortic valve
- #9 (taussig\* near/2 anomal\*)
- #10 (pulmon\* or aortic or subaortic or valve or mitral) next stenosis
- #11 ((aortic or aorta\*) near/3 coarctation\*)
- #12 (ventricular near/2 dysplasia\*)
- #13 (barth syndrome or cor triatriatum or cortriatriatum or triatrial heart\*)
- #14 (velo\* near/3 syndrome\*)
- #15 (myocardial bridging\* or crisscross heart\* or criss-cross heart\*)
- #16 (dextrocardia\* or kartagener\* syndrome or kartagener\* triad or siewert\* syndrome or primary ciliary dyskinesia)
- #17 "patent ductus arteriosus" or "scimitar syndrome" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch"
- #18 (ebstein\* anomaly or ebstein\* malformation\* or ectopia cordis)
- #19 (eisenmenger\* next (complex or syndrome))
- #20 (persistent truncus arteriosus or persistent ostium primum)
- #21 endocardial cushion defect\* or "atrioventricular canal"
- #22 (foramen oval\* or lutembacher\* syndrome)
- #23 (heart near/3 hypoplas\*)
- #24 ((noncompaction near/3 ventricular myocardium) or (non compaction near/3 ventricular myocardium))
- #25 ((leopard or multiple lentiginos) next syndrome\*)
- #26 levocardia or marfan\* syndrome
- #27 ((tetralogy or trilogy or syndrome) near/2 fallot\*) or cantrell\* or "shone's"



#28 (tricuspid atresia\* or valve atresia\* or pulmonary atresia or absent right atrioventricular connection)  
 #29 single ventricle physiology or GUCH or fontan procedure or cavopulmonary connection  
 #30 ((reparative or repair\*) near/2 (cardiac surgery or heart surgery))  
 #31 (bonnevie near/2 (syndrome\* or status)) or polynesian bronchiectas\*  
 #32 ((congenital\* or birth or born neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) and (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)):ti  
 #33 ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) near/5 (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)):ab  
 #34 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33  
 #35 MeSH descriptor: [Blood Transfusion] this term only  
 #36 MeSH descriptor: [Blood Component Transfusion] this term only  
 #37 MeSH descriptor: [Erythrocyte Transfusion] this term only  
 #38 MeSH descriptor: [Erythrocytes] this term only  
 #39 ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) near/3 (transfus\* or infus\* or hypertransfus\* or retransfus\*))  
 #40 ((transfus\* or retransfus\*) near/1 (trigger\* or level\* or threshold\* or rule\* or restrict\*))  
 #41 (transfusion\* near/2 (management or practice\* or polic\* or strateg\* or guideline\* or indication\* or protocol\* or criteri\* or autologous))  
 #42 ((blood near/2 management) or "blood sparing" or "cell salvage" or "blood support" or (blood near/2 requirement\*) or autotransfus\*)  
 #43 (red cell\* management or red cell\* sparing or red cell\* support or (red cell\* near/3 requirement\*))  
 #44 (blood near/1 need\*) or "whole blood"  
 #45 (leukodeplet\* or leukoreduc\* or leucodeplet\* or leucoreduc\* or leukofiltrat\* or leucofiltrat\*):ti  
 #46 ((leukocyte\* or leucocyte\*) near/2 (remov\* or deplet\* or reduc\* or poor or filtrat\*)):ti  
 #47 hemotransfus\* or haemotransfus\* or hemotherap\* or haemotherap\*  
 #48 (red cell\* or red blood cell\* or erythrocyte\* or whole blood or RBC\* or transfus\*):ti  
 #49 (bypass near/5 (prime or priming))  
 #50 ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) near/3 (exchang\* or replac\*))  
 #51 #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50  
 #52#34 and #51

## MEDLINE (Ovid)

1. exp Heart Defects, Congenital/
2. exp Heart Diseases/cn
3. ((heart\* or cardiac\* or coronary or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular) adj3 (congenital\* or defect\* or abnormal\* or anomal\*)):tw.
4. (digeorge adj (syndrome\* or anomal\* or sequenc\*)):tw.
5. (transpos\* adj3 (arteries or artery or vessel\*)):tw.
6. (alagille adj2 syndrome).tw.
7. (arteriohepatic dysplasia\* or gonadal dysgenesis or subdivided left atrium\* or cardiovertebral syndrome\* or pharyngeal pouch syndrome\* or thymic aplasia syndrome\* or conotruncal anomaly face syndrome).tw.
8. (hepatic hypoplasia or arteriohepatic dysplasia\* or turner\* syndrome or noonan syndrome or arteriohepatic dysplasia\* or bicuspid aortic valve).tw.
9. (taussig\* adj2 anomal\*):tw.
10. ((pulmon\* or aortic or subaortic or valve or mitral) adj stenosis).tw.
11. ((aortic or aorta\*) adj3 coarctation\*):tw.
12. (ventricular adj2 dysplasia\*):tw.
13. (barth syndrome or cor triatriatum or cortriatriatum or triatrial heart\*):tw.
14. (velo\* adj3 syndrome\*):tw.

15. (myocardial bridging\* or crisscross heart\* or criss-cross heart\*).tw.
16. (dextrocardia\* or kartagener\* syndrome or kartagener\* triad or siewert\* syndrome or primary ciliary dyskinesia).tw.
17. ("patent ductus arteriosus" or "scimitar syndrome" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch").tw.
18. (ebstein\* anomaly or ebstein\* malformation\* or ectopia cordis).tw.
19. (eisenmenger\* adj (complex or syndrome)).tw.
20. (persistent truncus arteriosus or persistent ostium primum).tw.
21. (endocardial cushion defect\* or atrioventricular canal).tw.
22. (foramen oval\* or lutebacher\* syndrome).tw.
23. (heart adj3 hypoplas\*).tw.
24. ((noncompaction adj3 ventricular myocardium) or (non compaction adj3 ventricular myocardium)).tw.
25. ((leopard or multiple lentigines) adj syndrome\*).tw.
26. (levocardia or marfan\* syndrome).tw.
27. (((tetralogy or trilogy or syndrome) adj2 fallot\*) or cantrell\* or shon?s).tw.
28. (tricuspid atresia\* or valve atresia\* or pulmonary atresia or absent right atrioventricular connection).tw.
29. (single ventricle physiology or GUCH or fontan procedure or cavopulmonary connection).tw.
30. ((reparative or repair\*) adj2 (cardiac surgery or heart surgery)).tw.
31. arterial switch.tw.
32. ((bonnevie adj2 (syndrome\* or status)) or polynesian bronchiectas\*).tw.
33. ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) and (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)).ti.
34. ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) adj5 (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)).ab.
35. or/1-34
36. BLOOD TRANSFUSION/
37. BLOOD COMPONENT TRANSFUSION/
38. ERYTHROCYTE TRANSFUSION/
39. ERYTHROCYTES/
40. ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) adj3 (transfus\* or infus\* or hypertransfus\* or retransfus\*)).ti,ab.
41. ((transfus\* or retransfus\*) adj1 (trigger\* or level\* or threshold\* or rule\* or restrict\*)).ti,ab.
42. ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) adj3 (exchang\* or replac\*)).tw.
43. (transfusion\* adj2 (management or practice\* or polic\* or strateg\* or guideline\* or indication\* or protocol\* or criteri\* or autologous)).ti,ab.
44. ((blood adj2 management) or blood sparing or cell salvage or cell saver\* or (blood adj2 salvag\*) or blood support or (blood adj2 requirement\*) or autotransfus\*).ti,ab.
45. (red cell\* management or red cell\* sparing or red cell\* support or (red cell\* adj3 requirement\*)).ti,ab.
46. ((blood adj1 need\*) or whole blood or blood product\* or blood component\*).ti,ab.
47. (leukodeplet\* or leukoreduc\* or leucodeplet\* or leucoreduc\* or leukofiltrat\* or leucofiltrat\*).ti.
48. ((leukocyte\* or leucocyte\*) adj2 (remov\* or deplet\* or reduc\* or poor or filtrat\*)).ti.
49. (hemotransfus\* or haemotransfus\* or hemotherap\* or haemotherap\*).tw.
50. (red cell\* or red blood cell\* or erythrocyte\* or whole blood or RBC\* or transfus\* or retransfus\*).ti.
51. (bypass adj5 (prime or priming)).tw.
52. or/36-51
53. 35 and 52
54. randomized controlled trial.pt.
55. controlled clinical trial.pt.
56. randomi\*.tw.
57. placebo.ab.
58. clinical trials as topic.sh.

59. randomly.ab.
60. groups.ab.
61. trial.ti.
62. or/54-61
63. exp animals/ not humans/
64. 62 not 63
65. 53 and 64

## EMBASE (Ovid)

1. exp Congenital Heart Disease/
2. exp Congenital Blood Vessel Malformation/
3. exp Heart Disease/cn
4. ((heart\* or cardiac\* or coronary or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular) adj3 (congenital\* or defect\* or abnormal\* or anomal\*)).tw.
5. (digeorge adj (syndrome\* or anomal\* or sequenc\*)).tw.
6. (transpos\* adj3 (arteries or artery or vessel\*)).tw.
7. (alagille adj2 syndrome).tw.
8. (arteriohepatic dysplasia\* or gonadal dysgenesis or subdivided left atrium\* or cardiovertebral syndrome\* or pharyngeal pouch syndrome\* or thymic aplasia syndrome\* or conotruncal anomaly face syndrome).tw.
9. (hepatic hypoplasia or arteriohepatic dysplasia\* or turner\* syndrome or noonan syndrome or arteriohepatic dysplasia\* or bicuspid aortic valve).tw.
10. (taussig\* adj2 anomal\* ).tw.
11. ((pulmon\* or aortic or subaortic or valve or mitral) adj stenosis).tw.
12. ((aortic or aorta\*) adj3 coarctation\* ).tw.
13. (ventricular adj2 dysplasia\* ).tw.
14. (barth syndrome or cor triatriatum or cortriatriatum or triatrial heart\* ).tw.
15. (velo\* adj3 syndrome\* ).tw.
16. (myocardial bridging\* or crisscross heart\* or criss-cross heart\* ).tw.
17. (dextrocardia\* or kartagener\* syndrome or kartagener\* triad or siewert\* syndrome or primary ciliary dyskinesia).tw.
18. ("patent ductus arteriosus" or "scimitar syndrome" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch").tw.
19. (ebstein\* anomaly or ebstein\* malformation\* or ectopia cordis).tw.
20. (eisenmenger\* adj (complex or syndrome)).tw.
21. (persistent truncus arteriosus or persistent ostium primum).tw.
22. (endocardial cushion defect\* or atrioventricular canal).tw.
23. (foramen oval\* or lutebacher\* syndrome).tw.
24. (heart adj3 hypoplasia\* ).tw.
25. ((noncompaction adj3 ventricular myocardium) or (non compaction adj3 ventricular myocardium)).tw.
26. ((leopard or multiple lentiginos) adj syndrome\* ).tw.
27. (levocardia or marfan\* syndrome).tw.
28. (((tetralogy or trilogi or syndrome) adj2 fallot\*) or cantrell\* or shon?s).tw.
29. (tricuspid atresia\* or valve atresia\* or pulmonary atresia or absent right atrioventricular connection).tw.
30. (single ventricle physiology or GUCH or fontan procedure or cavopulmonary connection).tw.
31. ((reparative or repair\*) adj2 (cardiac surgery or heart surgery)).tw.
32. arterial switch.tw.
33. ((bonnevie adj2 (syndrome\* or status)) or polynesian bronchiectas\* ).tw.
34. ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) and (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)).ti.
35. ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) adj5 (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or

intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU)).ab.

36. or/1-35

37. BLOOD TRANSFUSION/

38. BLOOD COMPONENT THERAPY/

39. ERYTHROCYTE TRANSFUSION/

40. ERYTHROCYTE/

41. ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) adj3 (transfus\* or infus\* or hypertransfus\* or retransfus\*)).ti,ab.

42. ((transfus\* or retransfus\*) adj1 (trigger\* or level\* or threshold\* or rule\* or restrict\*)).ti,ab.

43. (transfusion\* adj2 (management or practice\* or polic\* or strateg\* or guideline\* or indication\* or protocol\* or criteri\* or autologous)).ti,ab.

44. ((blood adj2 management) or blood sparing or cell salvage or cell saver\* or (blood adj2 salvag\*) or blood support or (blood adj2 requirement\*) or autotransfus\*).ti,ab.

45. (red cell\* management or red cell\* sparing or red cell\* support or (red cell\* adj3 requirement\*)).ti,ab.

46. ((blood adj1 need\*) or whole blood or blood product\* or blood component\*).ti,ab.

47. ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) adj3 (exchang\* or replac\*)).tw.

48. (leukodeplet\* or leukoreduc\* or leucodeplet\* or leucoreduc\* or leukofiltrat\* or leucofiltrat\*).ti.

49. ((leukocyte\* or leucocyte\*) adj2 (remov\* or deplet\* or reduc\* or poor or filtrat\*)).ti.

50. (hemotransfus\* or haemotransfus\* or hemotherap\* or haemotherap\*).tw.

51. (red cell\* or red blood cell\* or erythrocyte\* or whole blood or RBC\* or transfus\* or retransfus\*).ti.

52. (bypass adj5 (prime or priming)).tw.

53. or/37-52

54. 36 and 53

54. Randomized Controlled Trial/

55. Randomization/

56. Single Blind Procedure/

57. Double Blind Procedure/

58. Crossover Procedure/

59. Placebo/

60. exp Clinical Trial/

61. Prospective Study/

62. (randomi\* or double-blind\* or single-blind\* or RCT\*).tw.

63. (random\* adj2 (allocat\* or assign\* or divid\* or receiv\*)).tw.

64. (crossover\* or cross over\* or cross-over\* or placebo\*).tw.

65. ((treble or triple) adj blind\*).tw.

66. or/54-65

67. Case Study/

68. case report\*.tw.

69. (note or letter or editorial).pt.

70. or/67-69

71. 66 not 70

72. 54 and 71

73. limit 72 to embase

### PubMed (epublications only)

#1 ((blood[ti] OR erythrocyte\*[ti] OR red cell\*[ti] OR red blood cell\*[ti] OR RBC\*[ti]) AND (transfus\*[ti] OR infus\*[ti] OR hypertransfus\*[ti] OR retransfus\*[ti])) OR ((transfus\*[ti] OR retransfus\*[ti]) AND (trigger\*[ti] OR level\*[ti] OR threshold\*[ti] OR rule\*[ti] OR restrict\*[ti])) OR (transfusion\*[ti] AND (management[ti] OR practice\*[ti] OR polic\*[ti] OR strateg\*[ti] OR guideline\*[ti] OR indication\*[ti] OR protocol\*[ti] OR criteri\*[ti]))

#2 ("blood management" OR "blood sparing" OR "cell salvage" OR "blood salvage" OR "blood support" OR "blood requirement\*[ti]" OR "blood product\*" OR "blood component\*") OR (red cell\*[ti] AND (management[ti] OR sparing[ti] OR support[ti] OR requirement\*[ti])) OR ("need for blood"[ti] OR whole blood[ti] OR "use of blood"[ti])

#3 (leukodeplet\*[ti] OR leukoreduc\*[ti] OR leucodeplet\*[ti] OR leucoreduc\*[ti] OR leukofiltrat\*[ti] OR leucofiltrat\*[ti]) OR ((leukocyte\*[ti] OR leucocyte\*[ti]) AND (remov\*[ti] OR deplet\*[ti] OR reduc\*[ti] OR poor[ti] OR filtrat\*[ti])) OR (hemotransfus\*[ti] OR haemotransfus\*[ti] OR red cell\*[ti] OR red blood cell\*[ti] OR erythrocyte\*[ti] OR RBC\*[ti] OR transfus\*[ti]) OR (bypass[ti] AND (prime\*[ti] OR priming[ti]))

#4 #1 OR #2 OR #3

#5 ((congenital\*[ti] OR birth[ti] OR born[ti] OR neonat\*[ti] OR newborn\*[ti] OR infant\*[ti] OR pediatric\*[ti] OR paediatric\*[ti] OR child\*[ti] OR prematur\*[ti] OR defect\*[ti] OR abnormal\*[ti] OR anomal\*[ti]) AND (heart\*[ti] OR cardiac\*[ti] OR cardiomyopath\*[ti] OR coronary[ti] OR myocard\*[ti] OR septal\*[ti] OR aortopulmonary[ti] OR aorticopulmonary[ti] OR atrial[ti] OR ventricular[ti] OR intraventricular[ti] OR ventricle\*[ti] OR surg\*[ti] OR operat\*[ti] OR preoperat\*[ti] OR postoperat\*[ti] OR perioperat\*[ti] OR bypass\*[ti] OR intensive care[ti] OR critical care[ti] OR ICU[ti] OR PICU[ti]))

#6 #4 AND #5

#7 (random\* OR blind\* OR trial OR allocat\* OR assign\* OR "control group" OR groups OR intervention\*)

#8 #6 AND #7

#9 publisher[sb] NOT pubstatusnihms

#10 #8 AND #9

## CINAHL (EBSCO)

S1 (MH "Heart Defects, Congenital+")

S2 TI ((heart\* or cardiac\* or coronary or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular)

N3 (congenital\* or neonat\* or defect\* or abnormal\* or anomal\*)) OR AB ((heart\* or cardiac\* or coronary or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular) N3 (congenital\* or neonat\* or defect\* or abnormal\* or anomal\*))

S3 TI (transpos\* N3 (arteries or artery or vessel\*)) OR AB (transpos\* N3 (arteries or artery or vessel\*))

S4 TI (alagille N2 syndrome) OR AB (alagille N2 syndrome)

S5 TI ((hepatic hypoplasia) OR (arteriohepatic dysplasia\*)) OR (turner\* syndrome) OR (noonan syndrome) OR (arteriohepatic dysplasia\*) OR (bicuspid aortic valve)) OR AB ((hepatic hypoplasia) OR (arteriohepatic dysplasia\*) OR (turner\* syndrome) OR (noonan syndrome) OR (arteriohepatic dysplasia\*) OR (bicuspid aortic valve))

S6 TI ((pulmon\* or aortic or subaortic or valve or mitral) N1 stenosis) OR AB ((pulmon\* or aortic or subaortic or valve or mitral) N1 stenosis)

S7 TI ((aortic or aorta\*) N3 coarctation) OR AB ((aortic or aorta\*) N3 coarctation)

S8 TI (ventricular N2 dysplasia\*) OR AB (ventricular N2 dysplasia\*)

S9 TI ((barth syndrome) or (cor triatriatum) or cortriatriatum or (atrial heart\*)) OR AB ((barth syndrome) or (cor triatriatum) or cortriatriatum or (atrial heart\*))

S10 TI (coronary vessel\* N2 anomal\*) OR AB (coronary vessel\* N2 anomal\*)

S11 TX (myocardial bridging) or TX (arterial switch\*) or TX (crisscross heart\*) or TX (criss-cross heart\*)

S12 TI (dextrocardia\*) or TX (kartagener\* syndrome) or TX (kartagener\* triad) or TX (siewert\* syndrome) or TX (primary ciliary dyskinesia)

S13 TI ("patent ductus arteriosus" or "scimitar syndrome" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch") OR AB ("patent ductus arteriosus" or "scimitar syndrome" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch")

S14 TI ("ebstein\* anomaly" or "ebstein\* malformation\*" or "ectopia cordis") OR AB ("ebstein\* anomaly" or "ebstein\* malformation\*" or "ectopia cordis")

S15 TI (eisenmenger\* N1 (complex or syndrome)) OR AB (eisenmenger\* N1 (complex or syndrome))

S16 TI ("persistent truncus arteriosus" or "persistent ostium primum" or "endocardial cushion defect\*" or "atrioventricular canal" or "foramen oval\*" or "lutebacher\* syndrome") OR AB ("persistent truncus arteriosus" or "persistent ostium primum" or "endocardial cushion defect\*" or "atrioventricular canal" or "foramen oval\*" or "lutebacher\* syndrome")

S17 TI (heart N3 hypoplas\*) OR AB (heart N3 hypoplas\*)

S18 TI ((noncompaction N3 "ventricular myocardium") or TI ("non compaction" N3 "ventricular myocardium"))

S19 AB ((noncompaction N3 "ventricular myocardium") or AB ("non compaction" N3 "ventricular myocardium"))

S20 TI ((leopard or multiple lentigines) N1 syndrome\*) OR AB ((leopard or multiple lentigines) N1 syndrome\*)

S21 TI (levocardia or marfan\* syndrome) OR AB (levocardia or marfan\* syndrome)

S22 TI (((tetralogy or trilogy or syndrome) N2 fallot\*) or cantrell\* or shone?s) OR AB (((tetralogy or trilogy or syndrome) N2 fallot\*) or cantrell\* or shone?s)

S23 TI ((double outlet N3 ventricle) or taussig bing anomaly) OR AB ((double outlet N3 ventricle) or taussig bing anomaly)

S24 TI (tricuspid atresia\* or valve atresia\* or pulmonary atresia\* or absent right atrioventricular connection) OR AB (tricuspid atresia\* or valve atresia\* or pulmonary atresia\* or absent right atrioventricular connection)

S25 TI (single ventricle physiology or GUCH or fontan procedure or cavopulmonary connection) OR AB (single ventricle physiology or GUCH or fontan procedure or cavopulmonary connection)

S26 TI ((reparative or repair\*) N2 TX (cardiac surgery or heart surgery)) OR AB ((reparative or repair\*) N2 TX (cardiac surgery or heart surgery))

S27 TI ((bonnevie N2 TX (syndrome\* or status)) or polynesian bronchiectas\*) OR AB ((bonnevie N2 TX (syndrome\* or status)) or polynesian bronchiectas\*)

S28 TI ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) N5 (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU))

S29 AB ((congenital\* or birth or born or neonat\* or newborn\* or infant\* or pediatric\* or paediatric\* or child\* or prematur\*) N5 (heart\* or cardiac\* or cardiomyopath\* or coronary or myocard\* or septal\* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular or ventricle\* or surg\* or operat\* or preoperat\* or postoperat\* or perioperat\* or bypass\* or intensive care or critical care or ICU or PICU))

S30 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

S31 (MH BLOOD TRANSFUSION)

S32 (MH BLOOD COMPONENT TRANSFUSION)

S33 (MH ERYTHROCYTE TRANSFUSION)

S34 (MH ERYTHROCYTES)

S35 TI ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) N3 (transfus\* or infus\* or hypertransfus\* or retransfus\*)) OR AB ((blood or erythrocyte\* or red cell\* or red blood cell\* or RBC\*) N3 (transfus\* or infus\* or hypertransfus\* or retransfus\*))

S36 TI ((transfus\* or retransfus\*) N2 (trigger\* or level\* or threshold\* or rule\* or restrict\*)) OR AB ((transfus\* or retransfus\*) N2 (trigger\* or level\* or threshold\* or rule\* or restrict\*))

S37 TI (transfusion\* N2 (management or practice\* or polic\* or strateg\* or guideline\* or indication\* or protocol\* or criteri\* or autologous)) OR (transfusion\* N2 (management or practice\* or polic\* or strateg\* or guideline\* or indication\* or protocol\* or criteri\* or autologous))

S38 TI ((blood N2 management) or blood sparing or cell salvage or (blood N2 salvag\*) or blood support or (blood N2 requirement\*) or autotransfus\*) OR AB ((blood N2 management) or blood sparing or cell salvage or (blood N2 salvag\*) or blood support or (blood N2 requirement\*) or autotransfus\*)

S39 TI (red cell\* management or red cell\* sparing or red cell\* support or (red cell\* N3 requirement\*)) OR AB (red cell\* management or red cell\* sparing or red cell\* support or (red cell\* N3 requirement\*))

S40 TI ((blood N1 need\*) or whole blood or blood product\* or blood component\*) OR AB ((blood N1 need\*) or whole blood or blood product\* or blood component\*)

S41 TI (leukodeplet\* or leukoreduc\* or leucodeplet\* or leucoreduc\* or leukofiltrat\* or leucofiltrat\*)

S42 TI ((leukocyte\* or leucocyte\*) N2 (remov\* or deplet\* or reduc\* or poor or filtrat

S43 TI (hemotransfus\* or haemotransfus\*) OR AB (hemotransfus\* or haemotransfus\*)

S44 TI (red cell\* or red blood cell\* or erythrocyte\* or whole blood or RBC\* or transfus\*)

S45 TI (bypass N5 (prime or priming)) OR AB (bypass N5 (prime or priming))

S46 S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45

S47 S30 AND S46

S48 (MH "Clinical Trials+')

S49 PT Clinical trial

S50 TI ((controlled trial\*) or (clinical trial\*)) OR AB ((controlled trial\*) or (clinical trial\*))

S51 TI ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*)) OR AB ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*))

S52 TI randomi\* OR AB randomi\*

S53 (MH "Random Assignment')

S54 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S55 TI (random\* N2 (assign\* or allocat\*)) ) OR ( AB (random\* N2 (assign\* or allocat\*))  
 S56 TI placebo\* OR AB placebo\*  
 S57 (MH "Placebos")  
 S58 (MH "Quantitative Studies")  
 S59 S48 OR S49 OR S50 RO S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58  
 S60 S47 AND S59

## LILACS

(mh:("Blood Transfusion") OR mh:("Erythrocyte Transfusion") OR ti:(blood) OR ti:(erythrocyte\*) OR ti:(red cell\*) OR ti:(rbc\*) OR ti:(transfus\*) OR ti:(retransfus\*) OR ti:(cell salvage\*)) AND (congenital\* OR birth OR born OR neonat\* OR newborn\* OR infant\* OR pediatric\* OR paediatric\* OR child\* OR prematur\* OR defect\* OR abnormal\* OR anomal\* OR heart\* OR cardiac\* OR cardiomyopath\* OR coronary OR myocard\* OR septal\* OR aortopulmonary OR aorticopulmonary OR atrial OR ventricular OR intraventricular OR ventricle\* OR surg\* OR operat\* OR preoperat\* OR postoperat\* OR perioperat\* OR bypass\* OR "intensive care" OR "critical care" OR icu OR picu) AND db:("LILACS") AND type of study:("clinical trials" OR "systematic reviews")

## Transfusion Evidence Library

(blood OR erythrocyte\* OR red cell\* OR RBC\* OR transfus\* OR retransfus\* OR cell salvage) AND (congenital\* OR birth OR born OR neonat\* OR newborn\* OR infant\* OR pediatric\* OR paediatric\* OR child\* OR prematur\* OR defect\* OR abnormal\* OR anomal\*) AND (heart\* OR cardiac\* OR cardiomyopath\* OR coronary OR myocard\* OR septal\* OR aortopulmonary OR aorticopulmonary OR atrial OR ventricular OR intraventricular OR ventricle\* OR surg\* OR operat\* OR preoperat\* OR postoperat\* OR perioperat\* OR bypass\* OR "intensive care" OR "critical care" OR ICU OR PICU)

## Conference Proceedings Citation Index - Science (Web of Science)

(blood OR erythrocyte\* OR red cell\* OR RBC\* OR transfus\* OR retransfus\* OR cell salvage) AND (congenital\* OR birth OR born OR neonat\* OR newborn\* OR infant\* OR pediatric\* OR paediatric\* OR child\* OR prematur\* OR defect\* OR abnormal\* OR anomal\*) AND (heart\* OR cardiac\* OR cardiomyopath\* OR coronary OR myocard\* OR septal\* OR aortopulmonary OR aorticopulmonary OR atrial OR ventricular OR intraventricular OR ventricle\* OR surg\* OR operat\* OR preoperat\* OR postoperat\* OR perioperat\* OR bypass\* OR "intensive care" OR "critical care" OR ICU OR PICU) AND (random\* OR blind\* OR trial OR allocat\* OR assign\* OR "control group" OR groups OR intervention\*)

## INDMED

(blood OR erythrocyte\$ OR "red cell\$" OR RBC\$ OR transfus\$ OR retransfus\$ OR "cell salvage" OR autotransfus\$) AND ((congenital\$ OR birth OR neonat\$ OR newborn\$ OR infant\$ OR pediatric\$ OR paediatric\$ OR child\$ OR prematur\$ OR defect\$ OR abnormal\$ OR anomal\$) AND (heart\$ OR cardiac\$ OR cardiomyopath\$ OR coronary OR myocard\$ OR septal\$ OR aort\$ OR atrial OR ventric\$)) AND (random\$ OR blind\$ OR trial OR allocat\$ OR assign\$ OR control\$ OR groups)

## KOREAMED & PAKMEDINET (n.b. these databases require free-text searching using various combinations of the following search terms)

(blood OR erythrocyte\* OR "red cell\*" OR RBC\* OR transfus\* OR retransfus\* OR "cell salvage" OR autotransfus\*) AND (heart\* OR cardiac\* OR cardiomyopath\* OR coronary OR myocard\* OR septal\* OR aort\* OR atrial OR ventric\*) AND (random\* OR blind\* OR trial OR allocat\* OR assign\* OR control\* OR groups)

## ClinicalTrials.gov

Search Terms: infant OR infants OR neonate OR neonates OR neonatal OR newborn OR newborns OR congenital

Condition: heart OR cardiac OR cardiomyopathy OR coronary OR myocardial OR septal OR aortic OR atrial OR ventricular OR intraventricular OR aortopulmonary OR aorticopulmonary OR congenital

Intervention: blood OR erythrocyte OR "red cell" OR RBC OR transfusion OR retransfusion OR "cell salvage" OR autotransfusion OR bypass

Study Type: Interventional

## ISRCTN

(infant OR infants OR birth OR neonate OR neonates OR neonatal OR newborn OR newborns OR premature OR prematurity OR congenital) AND (transfusion OR transfused OR red cell OR red cells OR RBC OR RBCs) AND (randomized OR randomised OR randomly)

## WHO ICTRP

Condition: heart OR cardiac OR cardiomyopathy OR coronary OR myocardial OR septal OR aortic OR atrial OR ventricular OR intraventricular OR aortopulmonary OR aorticopulmonary OR congenital

Intervention: blood OR erythrocyte OR red cell OR RBC OR transfusion OR retransfusion OR autotransfusion OR bypass

## WHAT'S NEW

Last assessed as up-to-date: 11 December 2013.

Date	Event	Description
15 February 2013	Amended	We have added in a new (post hoc) outcome (biochemistry levels). Whilst there is only one of our included trials that measures this outcome, we are aware that this could be an important outcome both in this version of the review and in future updates. We overlooked the outcome at the protocol stage, hence its addition now

## CONTRIBUTIONS OF AUTHORS

Kirstin Wilkinson was the content expert for this review (congenital heart disease) and undertook the screening and selection of trials; data extraction; and assessment of risk of bias, analysis of results, and preparation of the protocol and final report.

Susan Brunskill was the methodological expert for this review and initially project managed the review, provided support and training to KW, undertook data extraction and assessment of risk bias, and provided support with data analysis and the initial preparation of the protocol and final report.

Carolyn Dorée was the information specialist who developed and implemented the search strategies, undertook the first sift of identified references, and contributed to the preparation of the protocol and final report.

Marielena Trivella was a methodological and statistical expert and provided support with data analysis and contributed to the preparation of the final report.

Ravi Gill was a content expert for this review (congenital heart disease) and contributed to the final report.

Mike Murphy was a content expert for this review (red cells and transfusion) and contributed to the preparation of the protocol and final report.



## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT

### Internal sources

- NHS Blood and Transplant, Research and Development, UK.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

February 2013: We have added in a new (post hoc) outcome, biochemistry levels. While there is only one of our included trials that measures this outcome, we are aware that this could be an important outcome both in this version of the review and in future updates. We overlooked the outcome at the protocol stage, hence its addition now. We have also updated the references in the background to included recently published, hence more up-to-date data.

## NOTES

None.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Cardiopulmonary Bypass; Erythrocyte Transfusion [\*adverse effects; mortality]; Heart Defects, Congenital [mortality; \*surgery]; Randomized Controlled Trials as Topic

### MeSH check words

Child; Humans; Infant, Newborn