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## **Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews (Review)**

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# Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews

Patricia M Fortin<sup>1</sup>, Sally Hopewell<sup>2</sup>, Lise J Estcourt<sup>3</sup>

<sup>1</sup>Sechelt, Canada. <sup>2</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK. <sup>3</sup>Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

Contact address: Lise J Estcourt, Haematology/Transfusion Medicine, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headington, Oxford, OX3 9BQ, UK. [lise.estcourt@nhsbt.nhs.uk](mailto:lise.estcourt@nhsbt.nhs.uk), [lise.estcourt@ndcls.ox.ac.uk](mailto:lise.estcourt@ndcls.ox.ac.uk).

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## ABSTRACT

### Background

Globally, sickle cell disease (SCD) is one of the commonest severe monogenic disorders, due to the inheritance of two abnormal haemoglobin (beta globin) genes. SCD can cause severe pain, significant end-organ damage, pulmonary complications, and premature death. Red blood cell (RBC) transfusions are used to treat complications of SCD, e.g. acute chest syndrome (ACS) (this often involves a single transfusion episode), or they can be part of a regular long-term transfusion programme to prevent SCD complications.

### Objectives

To summarize the evidence in Cochrane Reviews of the effectiveness and safety of RBC transfusions versus no transfusion, or restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) transfusion, for treating or preventing complications experienced by people with SCD.

### Methods

We included Cochrane Reviews of randomised or quasi-randomised controlled trials published in the Cochrane Database of Systematic Reviews, that addressed various SCD complications and had RBC transfusion as an intervention or comparator. We assessed the methodological quality of included reviews according to the AMSTAR quality assessment.

### Main results

We included 15 Cochrane Reviews, 10 of which had no included studies with an RBC transfusion intervention (five reported RCTs with other interventions; and five contained no studies). Five of the 15 reviews included participants randomised to RBC transfusion, but in one of these reviews only 10 participants were randomised with no usable data. Four reviews (nine trials with 1502 participants) reported data comparing short- or long-term RBC transfusions versus standard care, disease-modifying agents, a restrictive versus a liberal transfusion strategy and long-term RBC transfusions versus transfusions to treat complications. All reviews were of high quality according to AMSTAR quality assessment, however, the quality of the included trials was highly variable across outcomes. Trials were downgraded according to GRADE methodology for risk of bias, indirectness (most trials were conducted in children with HbSS), and imprecision (outcomes had wide confidence intervals).

In all four reviews and all comparisons there was little or no difference in the risk of death (very low-quality evidence). There were either no deaths or death was a rare event.

**Short-term RBC transfusion versus standard care** (one review: two trials, 434 participants, GRADE very low- to low-quality evidence)

In people undergoing low- to medium-risk surgery, RBC transfusions may decrease the risk of acute chest syndrome (ACS) in people with African haplotypes compared to standard care (low-quality evidence), but there was little or no difference in people with the Arabic haplotype (very-low quality evidence). There was also little or no difference in the risk of other SCD-related or transfusion-related complications (very-low quality evidence).

**Long-term RBC transfusion versus standard care** (two reviews: three trials, 405 participants, very low- to moderate-quality evidence)

In children and adolescents at high risk of stroke (abnormal transcranial doppler (TCD) velocities or silent cerebral infarct (SCI)), long-term RBC transfusions probably decrease the risk of stroke (moderate-quality evidence) and may decrease the risk of ACS and painful crisis compared to standard care (low-quality evidence). Long-term RBC transfusions may also decrease the risk of SCI in children with abnormal TCD velocities (low-quality evidence), but there may be little or no difference in the risk of SCI in children with normal TCD velocities and previous SCI (low-quality evidence).

In children and adolescents already receiving long-term RBC transfusions for preventing stroke, in comparison to standard care, continuing long-term RBC transfusions may reduce the risk of SCI (low-quality evidence) but we do not know whether there is a difference in the risk of stroke (very-low quality evidence). In children with normal TCD velocities and SCI there was little or no difference in the risk of alloimmunisation or transfusion reactions, but RBC transfusions may increase the risk of iron overload (low-quality evidence).

**Long-term RBC transfusion versus RBC transfusion to treat complications** (one review: one trial, 72 participants, very low- to low-quality evidence)

In pregnant women, long-term RBC transfusions may decrease the risk of painful crisis compared to transfusion for complications (low-quality evidence); but there may be little or no difference in the risk of other SCD-related complications or transfusion reactions (very-low quality evidence).

**RBC transfusion versus disease-modifying agents (hydroxyurea)** (two reviews: two trials; 254 participants, very low- to low-quality evidence)

For primary prevention of stroke in children, with abnormal TCD and no severe vasculopathy on magnetic resonance imaging/magnetic resonance angiography (MRI/MRA), who have received at least one year of RBC transfusions, we do not know whether there is a difference between RBC transfusion and disease-modifying agents in the risk of stroke; SCI; ACS; or painful crisis (very-low quality evidence). There may be little or no difference in the risk of iron overload (low-quality evidence).

Similarly, for secondary prevention of stroke in children and adolescents, we do not know whether there is a difference between these interventions in the risk of stroke; SCI; or ACS (very-low quality evidence); but hydroxyurea with phlebotomy may increase the risk of painful crisis and global SCD serious adverse events compared to RBC transfusion (low-quality evidence). There may be little or no difference in the risk of iron overload (low-quality evidence).

**Restrictive versus liberal RBC transfusion strategy** (one review: one trial; 230 participants, very low-quality evidence)

In people undergoing cholecystectomy, there was little or no difference between strategies in the risk of SCD-related or transfusion-related complications (very-low quality evidence).

### **Authors' conclusions**

This overview provides support from two high-quality Cochrane Reviews for the use of RBC transfusions in preventing stroke in children and adolescents at high risk of stroke (abnormal TCDs or SCI) and evidence that it may decrease the risk of SCI in children with abnormal TCD velocities. In addition RBC transfusions may reduce the risk of ACS and painful crisis in this population.

This overview highlights the lack of high-quality evidence in adults with SCD and the number of reviews that have no evidence for the use of RBC transfusions across a spectrum of SCD complications. Also of concern is the variable and often incomplete reporting of patient-relevant outcomes in the included trials such as SCD-related serious adverse events and quality of life.

## **PLAIN LANGUAGE SUMMARY**

**An overview of Cochrane Reviews on red blood cell transfusions to treat or prevent sickle cell disease-related complications**

Red blood cell transfusion to treat or prevent complications in sickle cell disease: an overview of Cochrane reviews (Review)  
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## Review question

To summarize the evidence in Cochrane Reviews of the effectiveness and safety of red blood cell (RBC) transfusions for treating or preventing complications experienced by people with sickle cell disease (SCD).

## Background

SCD is a serious inherited blood disorder where the RBCs, which carry oxygen around the body, develop abnormally. Normal RBCs are flexible and disc-shaped, but in SCD they can become rigid and crescent shaped. Sickled cells are not only less flexible than healthy RBCs, they are also stickier. This can lead to the blockage of blood vessels, resulting in tissue and organ damage and episodes of severe pain. The abnormal RBCs are more fragile and break apart, which leads to fewer of them, known as anaemia.

## Overview characteristics

We searched for Cochrane Reviews that analysed the data from randomised controlled trials (RCT; experiments that randomly allocate participants to one of two or more treatment groups), which looked at the effectiveness of RBC transfusions to prevent or treat SCD complications. This overview summarises the results of these reviews.

## Key results

15 reviews met the inclusion criteria for this overview. However, only four reviews (which included nine RCTs and 1052 participants) looked at the effects of RBC transfusion and had results that could be reported. In the four reviews there was no difference in the risk of death with any comparison. We found that long-term RBC transfusions compared to standard care, probably decrease the risk of stroke in children and adolescents at high risk of stroke (abnormal transcranial doppler (TCD) ultrasound (high blood flow to the brain) or a previous silent stroke (a stroke with no outward symptoms and where a person is typically unaware they have suffered a stroke)) and may also decrease their risk of painful crisis and acute chest syndrome. Red blood cell transfusions may also decrease the risk of silent stroke in children with abnormal TCD ultrasound when compared to standard care.

We found there was a lack of evidence for treating adults with SCD-related complications and that important outcomes, including quality of life were often not measured or reported.

## Quality of the reviews and evidence within reviews

All reviews included in this review were of high quality and met Cochrane standards for systematic reviews.

However, the quality of the trials included in the reviews was variable across the trials and in relation to the outcomes. The quality of the evidence within the trials was downgraded because trials had a high risk of bias, outcomes had imprecise measurements and much of the evidence applied only to children with HbSS disease.

People with SCD are living longer and we need more high-quality evidence on treating adults with SCD; as well as on the best treatment options, including the role of RBC transfusions, to treat SCD complications. We also need to improve and standardise the reporting of outcomes across trials.

# BACKGROUND

## Description of the condition

Sickle cell disease (SCD) is an inherited blood disorder, which can lead to life-threatening complications. People with SCD experience episodes of severe pain, and other complications including anaemia, end-organ damage, pulmonary complications, kid-

ney disease, and increased susceptibility to infections and stroke (Pleasant 2014). It is one of the most common severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes (Rees 2010). Populations originating from sub-Saharan Africa, the western hemisphere (South America, the Caribbean, and Central America), the Middle East, India and parts of the Mediterranean are predominantly affected. Reductions in infant and child mortality and increasing migration

from highly affected countries have made this a worldwide problem (Piel 2012). Over 12,500 people in the UK and 100,000 in the USA are estimated suffer from the disease (NICE 2010; Pleasants 2014). A recent study estimated that approximately 305,800 babies were born with SCD in 2010, of which two thirds were born in Africa, and this could increase by 25% to approximately 404,200 by 2050 (Piel 2012).

The term 'sickle cell disease' refers to all genotypes that cause the clinical syndrome. There are three main types of SCD. Sickle cell anaemia is the most common form of the disease (up to 70% of cases of SCD in people of African origin) and is due to the inheritance of two beta globin S ( $\beta$ S) alleles (haemoglobin (Hb)SS). The second most common genotype (up to 30% of cases in people of African origin) is haemoglobin SC disease (HbSC disease) it is due to the co-inheritance of the  $\beta$ S and  $\beta$ C alleles and tends to be a more moderate form of the disease. The third major type of SCD occurs when  $\beta$ S is inherited with a  $\beta$ -thalassaemia allele, causing HbS/ $\beta$ -thalassaemia. (Rees 2010). People who have inherited a thalassaemia null mutation (HbS $\beta^0$ ) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbS $\beta^+$  thalassaemia have a milder disorder. In high-income nations, people with SCD are expected to live into their 40's, 50's and beyond, whereas in low-income countries including some African nations it is estimated that between 50% to 90% of children born with HbSS die before their fifth birthday (Gravitz 2014; Grosse 2011).

People with SCD experience low oxygen levels, acidity and cellular dehydration, which cause the HbS molecules polymerise and begin to distort the red blood cells (RBCs) taking on the appearance of sickle-shaped cells. The main determinant of disease severity is the rate and extent of this HbS polymerisation (Rees 2010). This is exemplified by co-inheritance of genetic factors that affect the intracellular HbS or fetal haemoglobin concentration, e.g., the protective effects of co-inherited  $\alpha$ -thalassaemia (Rumaney 2014; Steinberg 2012) or hereditary persistence of fetal haemoglobin (Akinsheye 2011; Steinberg 2012). Sickling of RBCs results in two main events: blockage of blood flow resulting in organ and tissue ischaemia; and haemolytic anaemia (Sparkenbaugh 2013). Both of these processes are thought to lead to increased inflammation and an increased tendency to develop a clot (Frenette 2007; Rees 2010). Blockage of blood flow is mediated via a dynamic interaction between sticky HbS containing red cells, the vessel wall, and white cells (Rees 2010). Sickled RBCs also have a shorter lifespan of 10 to 12 days versus 120 days for normal RBCs due to intravascular and extravascular haemolysis, leading to anaemia (Kato 2006a). Chronic intravascular haemolysis leads to decreased levels of nitric oxide within the blood, development of pulmonary hypertension and ischaemic strokes (Kato 2006a; Kato 2006b).

## Description of the interventions

Individuals with SCD experience a variety of both acute and chronic complications as a result of the disease. Complications may be quite severe and include acute chest syndrome (ACS), acute cerebrovascular accident (CVA), acute and chronic pain, ocular or renal complications, chronic leg ulcers, priapism, avascular necrosis, pulmonary hypertension, and chronic respiratory and hepatobiliary complications (Expert Panel Report 2014). The course of the disease is highly variable with some people having a relatively mild course with fewer complications and longer survival and others having frequent severe complications and shortened survival. RBC transfusions are a mainstay of treatment in SCD and 90% of adults will have received at least one RBC transfusion (Chou 2013a).

RBC transfusions can be given to treat complications of SCD, e.g. ACS (this often involves a single transfusion episode), or they can be part of a regular long-term transfusion programme to prevent complications of SCD (Yawn 2014). People with SCD can be placed on a long-term transfusion programme to prevent recurrence of a complication they have already experienced or to prevent the first episode of a complication, e.g. stroke in children with abnormal transcranial dopplers (Adams 1998). Both a single transfusion episode or long-term transfusion programmes can use either a simple transfusion regimen or an exchange transfusion regimen (Josephson 2007). In addition to restrictive (to increase the total haemoglobin) or liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusions, other therapies may include drug therapy as an alternative to RBC transfusions such as hydroxyurea for anaemia, pain and ACS; or adjuvant RBC transfusion therapies such as analgesics for pain, oxygen for chest complications and fluid replacement for pain crisis.

RBC transfusions have reduced complications and improved the quality of life in people with SCD (Ware 2017); however, they can also cause adverse events (AEs) that are sometimes serious (Josephson 2007). The benefits of transfusion therapy must be balanced against risks including infections, iron overload, alloimmunisation, and acute or delayed haemolytic transfusion reactions (Chou 2013a, Chou 2013b; Porter 2013; Scheunemann 2010; Ubesie 2012).

## How the intervention might work

Transfusing normal RBCs to people with SCD who are anaemic, can increase the oxygen carrying capacity of the blood (Swerdlow 2006; Wagner 2007).

Sickled RBCs increase blood viscosity (resistance to flow) through intrinsic properties of the sickled cells, as well as through abnormal interactions of these cells with white cells, platelets, the vessel wall, and clotting factors. Transfusion of normal donor RBCs is used to mitigate these effects (Yawn 2014) and several regimens are used in current clinical practice. These include 'simple' transfusion in which normal RBCs are given to decrease anaemia without removal of the individual's blood. In people with SCD who

do not have severe anaemia simple RBC transfusions can cause hyperviscosity syndrome because they raise the haemoglobin, but only marginally lower the HbS percentage (Schmalzer 1987). Exchange transfusion involves removing some of the individual's own blood and transfusing allogeneic blood, thereby lowering the concentration of HbS through dilution. This reduces the effects of a given haemoglobin level on blood viscosity. A full exchange transfusion involves a full blood volume exchange by manual or automated apheresis, this allows for rapid lowering of the HbS level to 30% or less, and correction of anaemia. A partial (limited) exchange transfusion refers to manual removal of some of the individual's own blood, this is less effective in lowering the HbS level but is more easily performed when automated exchange is not available. In order to lower the HbS below 30%, repeat partial exchange transfusions may be necessary.

A restrictive (conservative) transfusion policy involves giving a simple transfusion to reach a pre-specified target haemoglobin.

A liberal (aggressive) transfusion policy involves giving a transfusion to reduce HbS percentage below a pre-specified threshold. In people with SCD with severe anaemia simple blood transfusions can lead to a significant reduction in HbS percentage without the need for an exchange transfusion. In a trial of people with SCD due to have an operation, 36% of participants randomised to the aggressive transfusion arm (to reduce HbS to 30% or below) were treated with a simple transfusion pre-operatively (Vichinsky 1995).

## Why it is important to do this overview

For people with SCD, RBC transfusions can reduce end-organ damage and be life saving by treating or preventing life-threatening complications (e.g. treating acute aplastic crisis or preventing strokes in children), but it may also be associated with serious complications. There are many indications for transfusion therapy in SCD; however, because of the inherent risks, an understanding of the evidence for its use for specific SCD complications is required. There is also wide variation in transfusion practices in SCD and some indications for transfusion therapy have been studied in randomised controlled trials (RCTs) and others based on observational studies or anecdotal evidence (Josephson 2007). Several Cochrane Reviews addressing SCD complications such as stroke (Estcourt 2017a), ACS (Alhashimi 2010), chronic chest complications (Estcourt 2016a), and preoperative transfusions (Estcourt 2016b) have been published. Providing an overview of these reviews will make the information more accessible for people with SCD and healthcare professionals.

In this overview we identified gaps in the evidence base to inform recommendations for new systematic reviews and clinical trials research. We also summarized evidence on reported outcomes to make recommendations for standardizing outcomes for new research and reviews. We appraised the reviews and summarized their quality and strength of evidence and considered both com-

mon indications for transfusion as well as indications where transfusion is not commonly indicated but may be occasionally used. We also considered the type of transfusion, restrictive or liberal, that may be most appropriate for a particular complication and whether transfusions are intermittent or long-term and used for prevention or treatment.

## OBJECTIVES

To summarize the evidence in Cochrane Reviews of the effectiveness and safety of RBC transfusions versus no transfusion, or restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) transfusion, for treating or preventing complications experienced by people with SCD.

## METHODS

### Criteria for considering reviews for inclusion

#### Types of reviews

We included Cochrane Reviews of RCTs or quasi-RCTs published in the *Cochrane Database of Systematic Reviews* part of the Cochrane Library, that reviewed the use of RBC transfusions for treatment or prevention of the various complications of SCD such as stroke, ACS, chronic chest complications.

#### Participants

We included Cochrane Reviews of people of all ages with known SCD.

#### Interventions

We included Cochrane Reviews that compare the following.

1. RBC transfusions versus no RBC transfusions
2. RBC transfusions plus standard care versus standard care (e.g. analgesia, intravenous fluids, oxygen)
3. RBC transfusions versus disease-modifying drug therapy (e.g. hydroxyurea)
4. Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy

### Primary outcomes

1. Mortality from any cause
2. Serious AEs (SAEs) as a result of SCD-related complications (e.g. neurological, ophthalmological, respiratory, orthopaedic, vascular, hepatic or renal complications, vaso-occlusive pain crisis, priapism, infections). We reported a summary count of total SAEs related to SCD-related complications, as well as reporting the types of complications that make up this summary measure (SAE defined in [Published notes](#)).
3. AEs (serious and non-serious) associated with transfusions (e.g. acute and delayed transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-associated dyspnoea, alloimmunisation, iron overload, problems of venous access). We reported a summary count of all adverse events related to transfusions, as well as reporting the types of complications that make up this summary measure.

### Secondary outcomes

1. Other AEs as a result of SCD-related complications
2. RBC transfusion requirement (number of units or mL required or number of RBC transfusion episodes)
3. Quality of life (using validated instruments)
4. Hospital length of stay including length of stay in critical care and hospital readmissions

### Search methods for identification of reviews

We performed a search of the *Cochrane Database of Systematic Reviews* (<http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/table-of-contents-cdsr.html>) to 04 February 2017. We used the text words: sickle cell disease, and blood transfusion in the title, abstract and keywords. We also used MeSH descriptors such as, 'anemia. sickle cell', 'erythrocyte transfusion'. We focused on retrieving all relevant published systematic reviews and identified published protocols (see [Appendix 1](#) for *Cochrane Database of Systematic Reviews* search strategy).

### Data collection and analysis

#### Selection of reviews

Two authors independently evaluated all reviews retrieved in the search for eligibility using the criteria listed in the [Criteria for considering reviews for inclusion](#) in the above section. We resolved conflicts through discussion to arrive at a consensus.

#### Data extraction and management

Two overview authors (LE, PF) independently extracted data. We extracted data on forms designed to summarise key characteristics of each review. We abstracted data on the objectives of each review, any diagnostic criteria, inclusion criteria (e.g. participants, details of intervention, comparison, outcomes, type of trials and length of follow-up), date of last search, frequency of updates, number of included trials, number of participants for each comparison and statistical outcome data. We also included narrative text of the results if meta-analyses using the Review Manager software were not available ([RevMan 2014](#)).

We extracted data from included reviews where possible, but we would have contacted the review authors or extracted data from the relevant trials ourselves if information was missing or unclear. Data obtained from authors or trials would have been integrated with data obtained from the review and the source of the data would have been highlighted. We contacted the relevant Cochrane review group when information was unclear.

We reported these data in a series of tables including 'Characteristics of included reviews' tables ([Table 1](#); [Table 2](#); [Table 3](#)). We reported details of the quality assessment of individual reviews using AMSTAR in tables ([Table 4](#); [Table 5](#); [Table 6](#)) as recommended in chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We also reported primary outcomes in a summary of findings overview table ([Figure 1](#)); and summary of findings tables based on the Grade assessments in the reviews ([Table 7](#); [Table 8](#); [Table 9](#)).



Figure 1.

Quality of evidence	Evidence of benefit		Evidence of harm	Direction of evidence				Evidence of no difference				Lack of evidence			
	Evidence of benefit		Evidence of harm	Direction of evidence				Evidence of no difference				Lack of evidence			
High-quality	⊕⊕⊕⊕		⊕⊕⊕⊕	⊕⊕⊕⊕				⊕⊕⊕⊕							
Moderate-quality	⊕⊕⊕○		⊕⊕⊕○	⊕⊕⊕○				⊕⊕⊕○							
Low-quality	⊕⊕○○		⊕⊕○○	⊕⊕○○				⊕⊕○○							
Very low-quality	⊕○○○		⊕○○○	⊕○○○				⊕○○○							
Cochrane review / Complication	Intervention			All-cause mortality for effect estimates see GRADE Table 7	SCD SAEs <sup>1</sup> for effect estimates see GRADE Table 8				Transfusion AEs <sup>2</sup> for effect estimates see GRADE Table 9						
					Global SAEs	Acute chest	Pain crisis	Neurological	Serious infection	Global AEs	Immune response	Transfusion reactions			
<b>Estcourt 2017</b> Primary and secondary stroke in people SCD	Long-term RBC transfusions vs. standard care	No previous long-term RBC transfusions	⊕○○○		⊕⊕○○	⊕⊕○○	⊕⊕○○			⊕○○○	⊕○○○				
		Previous long-term RBC transfusion	⊕○○○				⊕○○○								
	RBC transfusions vs disease- modifying agents (hydroxyurea)	Primary prevention	⊕○○○		⊕○○○	⊕○○○									
		Secondary prevention	⊕○○○	⊕⊕○○	⊕○○○	⊕⊕○○	⊕○○○								
		<b>Estcourt 2017a</b> Silent cerebral infarcts in people with SCD	Long-term RBC transfusions vs. standard care	Abnormal TCD velocities	⊕○○○		⊕⊕○○	⊕○○○	⊕⊕○○						
Normalised TCD velocities	⊕○○○						⊕⊕○○								
Normal TCD velocities	⊕○○○				⊕⊕○○	⊕⊕○○	⊕⊕○○			⊕○○○	⊕○○○				
RBC transfusions versus disease- modifying agents (hydroxyurea)	Primary prevention		⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○								
<b>Estcourt 2016</b> Preoperative blood transfusions for people with SCD	Restrictive vs liberal RBC transfusion Short term RBC transfusion vs standard care	People with SCD undergoing cholecystectomy	⊕○○○		⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○				
		African Haplotype	⊕○○○		⊕⊕○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○				
		Arabic Haplotype	⊕○○○		⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○	⊕○○○				
<b>Okusanya 2016</b> Prophylactic vs selective RBC transfusion- pregnancy	Long-term RBC transfusions vs transfusions to treat complications in Pregnant women with SCD		⊕○○○		⊕○○○	⊕⊕○○		⊕○○○			⊕○○○				
<b>Dastgiri 2016</b> Acute chest syndrome in people with SCD	RBC transfusion vs. standard care														
<b>Estcourt 2016</b> Chronic chest complication in SCD	RBC transfusion vs. standard care														
<b>Marti-Carvajal 2009</b> Painful sickle cell crisis during pregnancy	Various interventions vs. each other placebo standard care														
<b>Marti-Carvajal 2015</b> Intrahepatic cholestasis in people with SCD	Various interventions vs. each other and standard care														
<b>Oringanje 2016</b> Hematopoietic stem cell transplantation for people with SCD	Stem cell transplant versus each other or supportive care														
<b>Owusu-Ofori 2015</b> Acute sequestration crises in people SCD	Splenectomy vs. conservative management														
<b>Roy 2017</b> Chronic kidney disease in people with SCD	BT Hydroxyurea, ACEI vs. each other														
<b>Chinegwundoh 2010</b> Priapism in boys and men with SCD	Any treatment vs. any treatment														
<b>Marti-Carvajal 2014</b> Leg ulcers in people with SCD	Various interventions vs. any other interventions														
<b>Marti-Carvajal 2014</b> Avascular necrosis of bone in people with SCD	Surgical and non-surgical vs. each other or standard care														
<b>Oniyangi 2015</b> Phytomedicines for SCD	Phytomedicine vs placebo or standard care (BT and Hydroxyurea)														
<sup>1</sup> Includes neurological, ophthalmological, respiratory, orthopaedic, vascular, hepatic or renal complications, vaso-occlusive pain crisis, priapism, infections															
<sup>2</sup> Includes serious and non-serious adverse events associated with transfusions (e.g. acute and delayed transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-associated dyspnoea, alloimmunisation, iron overload, problems of venous access)															

## Assessment of methodological quality of included reviews

### Methodological quality of included reviews

Two overview authors (LE, PF) assessed the methodological quality of the included reviews using the 11 domains in AMSTAR (Shea 2007; Appendix 2) and used these domains to interpret the results of the review. We resolved any differences through discussion or third party adjudication (SH). Rather than providing a numerical summary of the ratings we provided a judgement or copied text from the review for each domain to support the quality rating of the included reviews. We did not exclude reviews based on their methodological quality. We did not conduct sensitivity analyses to explore the consequences of combining reviews of varying methodological quality because all included reviews are Cochrane Reviews, we did not expect significant overlap between comparisons. A recent systematic review of the measurement properties of AMSTAR found that the interrater reliability of AMSTAR was very satisfactory (Pieper 2015). As more guidance is provided for its use, and additional validity studies that link systematic review methodological quality to the strength of conclusions (Pieper 2015), we will use AMSTAR in future updates of this overview until a more reliable tool becomes available. AMSTAR domains include:

1. an a priori design;
2. duplicate review and data abstraction;
3. a comprehensive search was performed;
4. status of publication used as an inclusion criteria;
5. a list of included and excluded studies provided;
6. characteristics of included studies provided;
7. scientific quality was assessed and documented;
8. scientific quality was used appropriately in formulating conclusions;
9. appropriate methods were used to combine the findings of trials;
10. publication bias was assessed;
11. conflict of interest included.

### Quality of evidence in included reviews

Two overview authors (LE, PF) assessed and summarized the quality of evidence included in the summary of findings tables and the risk of bias tables according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and recommendations in the *Cochrane Handbook of Systematic Reviews of Interventions*, respectively (Balslem 2011; Higgins 2011a; Schünemann 2011). Assessments included information on

outcomes across studies and based on trial design, directness of evidence, precision and consistency of results, and publication bias. Where possible we graded the outcomes based on assessments provided in the original reviews. We resolved any differences through discussion or third party adjudication (SH).

### Data synthesis

Our unit of analysis was the included systematic reviews. We presented all statistical outcome data if available, if this was not possible we presented data as a narrative synthesis. We reported the evidence for each intervention from the reviews using the GRADE approach (Balslem 2011; Schünemann 2011). The data available in the reviews, determined the comparisons presented.

We included a Summary of findings overview table (Figure 1); and summary of findings tables for the three primary outcomes in this overview, for each intervention (Table 7; Table 8; Table 9). These are in a format similar to the 'Summary of findings' table as recommended in chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Where possible, we classified data from reviews into subgroups based on:

- the indication for RBC transfusions for preventing or treating SCD complications;
- acute or chronic RBC transfusions;
- restrictive (to increase the total haemoglobin) or liberal (to decrease the haemoglobin S level below a specified percentage) transfusion;
- by age of participants (children, adolescents, adults);
- participant characteristics (i.e. pregnant, undergoing surgery, type of SCD).

As planned, we did not conduct any indirect comparisons or network meta-analyses.

## RESULTS

### Results of the search

We searched the Cochrane Database of Systematic Reviews on 04 February 2017 and retrieved 127 reviews. Two review authors (LE, PF) excluded 100 reviews that were not relevant. We examined the full text of 27 Cochrane Reviews and excluded another 12 reviews:

- Nine reviews did not include RBC transfusion as an intervention or comparator (Al Hajeri 2016; Alhashimi 2010; Jones 2001; Knight-Madden 2014; Martí-Carvajal 2012; Martí-Carvajal 2015b; Nagalla 2012; Okomo 2015; van Zuuren 2013)

- Three reviews did not include people with SCD (Carson 2012; Dodd 2004; Meremikwu 1999).

We included 15 reviews that addressed various SCD complications and where RBC transfusion was an intervention or comparator (Chinegwundoh 2004; Dastgiri 2016; Estcourt 2016a; Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Martí-Carvajal 2009; Martí-Carvajal 2014; Martí-Carvajal 2015a; Martí-Carvajal 2016; Okusanya 2016; Oniyangi 2015; Oringanje 2016; Owusu-Ofori 2015; Roy 2017).

Five reviews included RCTs with an RBC transfusion intervention for the following complications: primary and secondary stroke (Estcourt 2017a); silent cerebral infarcts (SCI) (Estcourt 2017b); preoperative transfusion (Estcourt 2016b); prevention of SCD complications in pregnancy (Okusanya 2016); and ACS (Dastgiri 2016) (Table 1).

10 reviews had no RCTs with an RBC transfusion intervention. Five of these reviews included RCTs with other interventions for the following complications: chronic kidney disease (Roy 2017); priapism (Chinegwundoh 2004); leg ulcers (Martí-Carvajal 2014); avascular necrosis (Martí-Carvajal 2016); and phytomedicines (Oniyangi 2015) (Table 2). Five reviews contained no RCTs that met the inclusion criteria for the following complications: chronic chest complications (Estcourt 2016a); painful crisis in pregnancy (Martí-Carvajal 2009); intrahepatic cholestasis (Martí-Carvajal 2015a); hematopoietic stem cell transplantation (Oringanje 2016); and acute splenic sequestration crisis (Owusu-Ofori 2015) (Table 3).

## Description of included reviews

The 15 reviews were published between 2004 to 2017. Three were new reviews (Estcourt 2017b; Martí-Carvajal 2015a; Roy 2017), and the remainder were updated reviews.

In this overview we have focused on describing the five reviews that included RCTs with an intervention of RBC transfusion (Estcourt 2017a; Estcourt 2017b; Estcourt 2016b; Okusanya 2016; Dastgiri 2016) (Table 1).

We have presented the review characteristics of the remaining 10 reviews with no RBC transfusion intervention or no included trials in additional tables (Table 2; Table 3). We rated these 10 reviews as high quality according to AMSTAR quality assessment (Table 5, Table 6).

## Study design

All five reviews included RCTs, one review also included quasi-RCTs (Estcourt 2016b).

One review (on ACS) included one multicentre trial that enrolled 237 people, of which only 10 participants met the inclusion criteria for randomisation, the remaining 227 participants were recruited to an observational arm (Dastgiri 2016). The review authors could not extract any data from the randomised participants in the trial.

The other four reviews contained nine unique trials, of parallel group design, with two reviews reporting on the same trials (Estcourt 2017a; Estcourt 2017b). In one review (surgery) containing three trials participant follow-up was 30 days (Estcourt 2016b). In the two reviews with the same five trials (participants at high risk of stroke or SCIs), follow-up ranged from six months to a median of three years (Estcourt 2017a; Estcourt 2017b); and the other review (in pregnant women), included one trial with a follow-up of 21.5 to 24.5 weeks of prenatal care (Okusanya 2016).

## Included participants

A total of 1512 participants were included in the five reviews. Two reviews (on stroke and SCIs) included the same five trials with 659 participants (Estcourt 2017a; Estcourt 2017b). In one review (surgery), one trial reported on 551 trial participants; however, the review authors report on subgroups of 230 participants undergoing cholecystectomy, and 107 participants undergoing tonsillectomy or adenoidectomy, the trial re-randomised participants creating unit of analysis issues. The review authors did not combine the two subgroups as it was unknown if any of the participants had both surgeries. This review included three trials with 771 participants (Estcourt 2016b). One review (on pregnancy) included one trial with 72 women (Okusanya 2016). One review (on ACS) included only 10 participants (Dastgiri 2016).

In two reviews, participants in the included trials were either children or children and adolescents (mean ages eight to nine years) (Estcourt 2017a; Estcourt 2017b). Two reviews included trials with children and adults (Dastgiri 2016; Estcourt 2016b). One review included pregnant women who had a mean age of 23 years (Okusanya 2016).

In two reviews, trials included only HbSS or HbS $\beta^0$  phenotypes and the majority of participants were HbSS phenotype (Estcourt 2017a; Estcourt 2017b). In one review with three trials, participants in one trial were all diagnosed with HbSS disease; in another trial some participants were diagnosed with HbS $\beta^0$  but the majority of participants had HbSS; and in one trial, although the majority of participants had HbSS, a substantial number also had HbS $\beta^0$  (n = 74) and the trial also included a small proportion of participants with HbS $\beta^+$  and HbSC disease (Estcourt 2016b). In the Okusanya review all women in the one trial had HbSS disease (Okusanya 2016).

## Interventions

All five reviews had an RBC transfusion group. Two reviews addressing stroke and SCI respectively, had an RBC transfusion arm versus standard care (n = 405) or hydroxyurea (n = 254) (Estcourt 2017a; Estcourt 2017b). One review included an RBC transfusion arm versus standard care (n = 10) (Dastgiri 2016). One review on preoperative RBC transfusions included 337 participants from one trial which compared a liberal RBC transfusion regimen,

designed to decrease the haemoglobin S level to less than 30%, to a restrictive RBC transfusion regimen, designed to increase the haemoglobin level to 100 g/L. This review also included two trials with 434 participants which compared a preoperative RBC transfusion arm (simple or exchange) to standard care (Estcourt 2016b). In one review with 72 pregnant women, long-term RBC transfusions to optimise haemoglobin concentration to a specified level were compared to short-term (emergency) RBC transfusions to treat specific complications or a critically low level of haemoglobin (Okusanya 2016).

## Methodological quality of included reviews

### Quality of included reviews (AMSTAR)

All five reviews that included an RBC transfusion group were high quality according to AMSTAR quality assessment (Table 4). The five reviews provided: an a priori design and published Cochrane Protocol; comprehensive searches of the relevant group's specialised registers and other databases and searches of clinical trials and grey literature. All reviews contained tables of included and excluded trials and review authors rated trial quality using the Cochrane Risk of Bias tool and included GRADE summary of findings tables - except in the Dastgiri review, as there were no data to report (Dastgiri 2016). Discussion and conclusions were appropriate to the quality of evidence and the review authors used appropriate methods to combine findings, analyse data or provide a narrative review of outcomes. There were too few trials in the reviews to assess publication bias.

### Quality of evidence in included reviews (GRADE)

Review authors, in accordance with GRADE criteria, rated the quality of evidence as very-low to moderate across different outcomes in two reviews (Estcourt 2017a; Estcourt 2017b). In the Estcourt 2016 review, review authors rated the quality of evidence as very-low to low across all outcomes, according to GRADE criteria (Estcourt 2016b). In the Okusanya review, review authors rated the one included trial as very-low quality evidence according to GRADE criteria (Okusanya 2016). In the Dastgiri review, review authors rated the risk of bias as unclear in all domains due to incomplete reporting and they could not include a summary of findings table as there were no data to extract (Dastgiri 2016).

### Effect of interventions

See: summary of findings overview table (Figure 1)

In the Dastgiri review only 10 participants were included in the randomised part of the study and no data were reported on any of the review outcomes (Dastgiri 2016).

We have reported the outcomes for this overview, for the other four reviews which include 1502 participants and nine RCTs with an RBC intervention (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016). As well as a summary of findings overview table (Figure 1), we have included detailed summary of findings tables for the following outcomes: mortality (Table 7); SCD-related SAEs (Table 8); and transfusion-related AEs (Table 9).

## Primary outcomes

### I. Mortality from any cause

(see Mortality: summary of findings Table 7)

Four reviews reported this outcome (nine trials; 1502 participants) (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016).

#### RBC transfusions versus standard care

All four reviews (six trials, 955 participants) compared short- or long-term RBC transfusion to standard care (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016). There was little or no evidence of a difference in all-cause mortality; however, this evidence was very low-quality according to GRADE criteria. There were either no deaths (short-term transfusion) or death was a rare event (long-term transfusion) (Table 7).

#### RBC transfusions versus disease-modifying agents

Two reviews (two trials; 254 participants) compared RBC transfusion versus hydroxyurea for primary or secondary prevention of stroke in children or adolescents (Estcourt 2017a; Estcourt 2017b). There was little or no evidence of a difference in all-cause mortality; however, this evidence was very low-quality according to GRADE criteria. There were either no deaths (primary prevention) or death was a rare event (secondary prevention) (Table 7).

#### Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy

One review (one trial; 230 participants) compared a restrictive to a liberal RBC transfusion strategy in people undergoing cholecystectomy (Estcourt 2016b). There was little or no evidence of a difference in all-cause mortality; however, this evidence was very low-quality according to GRADE criteria. There were no deaths (Table 7).

## 2. Serious adverse events as a result of SCD-related complications

(see SCD-related SAEs: summary of findings (Table 8))

Four reviews reported this outcome (nine trials; 1502 participants) (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016).

### RBC transfusions versus standard care

#### Short-term

One review (two trials, 434 participants) compared short-term RBC transfusion versus standard care in people undergoing low- to medium-risk surgery (Estcourt 2016b). There was little or no difference in the risk of neurological complications; painful crises; serious infections; and renal complications; however, this evidence was very low-quality according to GRADE criteria. RBC transfusions may decrease the risk of ACS in people with SCD and African haplotypes, RR 0.11 (95% CI 0.01 to 0.80) (one trial, 65 participants, GRADE low-quality evidence); but there was little or no difference in the risk of ACS in individuals with Arabic haplotypes (one trial, 369 participants, GRADE very low-quality evidence) (Table 8).

#### Long-term

Two reviews (three trials, 405 participants) compared long-term RBC transfusion versus standard care in children and adolescents at high risk of stroke (Estcourt 2017a; Estcourt 2017b). In children who have not previously received long-term RBC transfusions and at high risk of stroke (abnormal TCDs or SCI; two trials; 326 participants), long-term RBC transfusions decrease the risk of stroke, RR 0.12 (95% CI 0.03 to 0.49) (GRADE moderate-quality evidence). RBC transfusion may also decrease the risk of ACS, RR 0.24 (95% CI 0.12 to 0.48) (GRADE low-quality evidence); and painful crisis, RR 0.62 (95% CI 0.46 to 0.84) (GRADE low-quality evidence) (Estcourt 2017a) (Table 8). Long-term RBC transfusions in children with abnormal TCD velocities, may also decrease the risk of SCIs, RR 0.11 (95% CI 0.02 to 0.86) (one trial, 124 participants, GRADE low-quality evidence) and the risk of ACS, RR 0.30 (95% CI 0.11 to 0.87) (one trial, 130 participants, GRADE low-quality evidence), but there was little or no difference in children with normal TCD velocities on the risk of SCIs (one trial, 196 participants, GRADE low-quality evidence) (Estcourt 2017b) (Table 8). In children and adolescents who have received previous long-term RBC transfusions (one trial, 79 participants), there was little or no difference in the risk of clinical stroke, but this evidence was graded as very low-quality (Estcourt 2017a). Continuing long-term RBC transfusions (one trial, 77 participants) may reduce the incidence of SCI, RR 0.29 (95% CI

0.09 to 0.97) (GRADE low-quality evidence) (Estcourt 2017b) (Table 8).

One review (one trial, 72 participants) compared long-term RBC transfusions versus RBC transfusions to treat complications in pregnant women (Okusanya 2016). Long-term RBC transfusions may decrease the risk of painful crisis, RR 0.28 (95% CI 0.12 to 0.67) (GRADE low-quality evidence); but there was little or no difference on the risk of other SCD-related complications (ACS; renal complications; serious infection); however, this evidence was very low-quality according to GRADE criteria (Table 8).

### RBC transfusions versus disease-modifying agents

Two reviews (two trials; 254 participants) compared RBC transfusion versus hydroxyurea for primary or secondary prevention of stroke in children or adolescents (Estcourt 2017a; Estcourt 2017b).

For primary prevention of stroke in children with abnormal TCD velocities and no severe vasculopathy on MRI/MRA (one trial, 121 participants), there was little or no difference in the risk of SCD-related complications (stroke; SCI; global SAEs; ACS; painful crisis); however, this evidence was very low-quality according to GRADE criteria (Table 8).

In secondary prevention (one trial, 133 participants), hydroxyurea and phlebotomy may increase the risk of painful crisis, RR 3.15 (95% CI 1.23 to 8.11) and global SCD SAEs, RR 3.10 (95% CI 1.42 to 6.75) (GRADE low-quality evidence) (Table 8), but there was little or no difference in the risk of stroke, SCI or ACS (this evidence was very low-quality according to GRADE criteria Table 8).

### Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy

One review (one trial; 230 participants) compared a restrictive to a liberal RBC transfusion strategy in people undergoing cholecystectomy (results for the tonsillectomy/adenoidectomy groups are similar) (Estcourt 2016b). There was little or no difference on the risk of SCD-related complications (neurological; renal; ACS; painful crisis; serious infection); however, this evidence was very low-quality according to GRADE criteria (Table 8).

## 3. Adverse events (serious and non-serious) associated with transfusions

(see transfusion-related AEs (serious and non-serious): summary of findings (Table 9))

This outcome is reported in four reviews (nine trials; 1502 participants) (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016).



## RBC transfusions versus standard care

### Short-term

One review (two trials, 434 participants) compared short-term RBC transfusion versus standard care in people undergoing low- to medium-risk surgery (Estcourt 2016b). There was little or no difference in the risk of transfusion-related complications (alloimmunisation; serious transfusion complications; transfusion reactions); however, this evidence was very low-quality according to GRADE criteria (Table 9).

### Long-term

Two reviews (three trials, 405 participants) compared long-term RBC transfusion versus standard care in children and adolescents at high risk of stroke (Estcourt 2017a; Estcourt 2017b). In children with no previous long-term RBC transfusions with normal TCD velocities and silent stroke (one trial, 121 participants), there was little or no difference in the risk of alloimmunisation or transfusion reactions; however, the evidence was very low-quality according to GRADE criteria. However, RBC transfusions may increase the risk of iron overload, incidence rate ratio 14.42 (95% CI 5.41 to 875.17) (GRADE low-quality evidence) (Table 9). In children and adolescents with abnormal or normalised TCD velocities (two trials, 209 participants) there is no effect estimate for alloimmunisation, transfusion reactions, and iron overload as no comparative numbers were provided.

One review (one trial, 72 participants) compared long-term RBC transfusions versus RBC transfusions to treat complications in pregnant women (Okusanya 2016) and there was little or no difference in the risk of transfusion reactions, however, this evidence was very low-quality according to GRADE criteria (Table 9).

## RBC transfusions versus disease-modifying agents

Two reviews (two trials; 254 participants) compared RBC transfusion and chelation versus switching to hydroxyurea and phlebotomy used for primary or secondary prevention of stroke in children or adolescents (Estcourt 2017a; Estcourt 2017b) and there was little or no difference in liver iron concentrations, this evidence was low-quality according to GRADE criteria (Table 9).

### Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy

One review (one trial; 230 participants) compared a restrictive to a liberal RBC transfusion strategy in people undergoing cholecystectomy (Estcourt 2016b). There was little or no difference in the risk of alloimmunisation; transfusion reactions; or any transfusion

complication, however, this evidence was very low-quality according to GRADE criteria (Table 9).

## Secondary outcomes

### 1. Other adverse events as a result of SCD-related complications

This outcome was not reported in the short-term RBC transfusions and the restrictive transfusion versus liberal RBC transfusion comparisons; three reviews reported this outcome with 838 participants (Estcourt 2017a; Estcourt 2017b; Okusanya 2016).

## RBC transfusions versus standard care

### Long-term

Two reviews (three trials, 405 participants) compared long-term RBC transfusion versus standard care in children and adolescents at high risk of stroke (Estcourt 2017a; Estcourt 2017b). In children with no previous long-term RBC transfusions with normal TCD velocities and silent stroke, RBC transfusions may reduce the risk of priapism (incidence rate ratio 0.13 (95% CI 0.03 to 0.55) (one trial, 112 participants); symptomatic avascular necrosis of the hip (incidence rate ratio 0.22 (95% CI 0.05 to 0.85) (one trial, 196 participants) (Estcourt 2017a; Estcourt 2017b).

One review (one trial, 72 participants) compared long-term RBC transfusions versus RBC transfusions to treat complications in pregnant women (Okusanya 2016) and there was little or no difference in the risk in the occurrence of splenic sequestration, RR 0.33 (95%CI 0.01 to 7.92) (GRADE low-quality evidence).

## RBC transfusions versus disease-modifying agents

Two reviews (two trials; 254 participants) compared RBC transfusion versus hydroxyurea used for primary or secondary prevention of stroke in children or adolescents (Estcourt 2017a; Estcourt 2017b) and there was little or no difference in the risk of TIA, however this evidence was very low-quality according to GRADE criteria.

### 2. RBC transfusion requirement

RBC transfusion requirement was not reported in the RBC transfusion versus disease-modifying agents comparison. Four reviews reported this outcome (five trials, 527 participants) (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Okusanya 2016).

### RBC transfusions versus standard care

#### Short-term

One review (two trials, 434 participants) compared short-term RBC transfusion versus standard care in people undergoing low to medium risk surgery (Estcourt 2016b).

In participants that received an intraoperative or postoperative transfusion (one trial, four participants transfused; 12 participants no transfusion) there was little or no difference in the number of units administered per transfusion.

#### Long-term

Two reviews (three trials, 405 participants) compared long-term RBC transfusion versus standard care in children and adolescents at high risk of stroke (Estcourt 2017a; Estcourt 2017b). In children and adolescents with abnormal TCD velocities (one trial, 130 participants), 1521 transfusions were given; and children and adolescents with normalised TCD velocities and previous long-term RBC transfusions (one trial, 79 participants) 1070 transfusions were given.

One review (one trial, 72 participants) compared long-term RBC transfusions versus RBC transfusions to treat complications in pregnant women (Okusanya 2016); 432 units (with mean of 12 units) were transfused in women receiving long-term RBC transfusions and 108 units (with mean of 3 units) in women receiving RBC transfusions to treat complications. Women receiving long-term RBC transfusions received more RBC units.

### Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy

In one review (one trial, 230 participants) (Estcourt 2016b) in people undergoing cholecystectomy, there was an increase in the number of red cell units transfused in the liberal RBC transfusion arm, MD 2.70 units (95% CI 2.10 to 3.30); however, this evidence was very low-quality according to GRADE criteria.

### 3. Quality of life

Quality of life was not reported for RBC transfusions versus disease-modifying agents, for restrictive RBC transfusion versus liberal RBC transfusion, or for long-term RBC transfusions versus RBC transfusions to treat complications.

This outcome is reported in three reviews and includes 215 participants (Estcourt 2016b; Estcourt 2017a; Estcourt 2017b).

### RBC transfusions versus standard care

#### Short-term

One review (two trials, 434 participants) compared short-term RBC transfusion versus standard care in people undergoing low-

to medium-risk surgery (Estcourt 2016b), the mean health-related quality of life scores were higher in the short-term RBC transfusion group when controlling for baseline EQ-5D, MD 0.024 (95% CI -0.093 to 0.141) (one trial, 19 participants, included data on one re-randomised participant, evidence not GRADE assessed in review), analysis performed by trial authors.

#### Long-term

Two reviews (three trials, 405 participants) compared long-term RBC transfusion versus standard care in children and adolescents at high risk of stroke (Estcourt 2017a; Estcourt 2017b). In children with normal TCD velocities and silent stroke, quality of life was measured on the Child Health Questionnaire Parent Form 50 (CHQ-PF50) completed at baseline and at the occurrence of an overt stroke or at trial exit at 36 months. It is not known what the minimal clinically important differences are for the CHQ-PF50. Long-term RBC transfusions may increase the quality of life, MD -0.54 (95% CI -0.92 to -0.17) (one trial, 196 participants, GRADE low-quality evidence) analysis performed by the trial authors.

### 4. Hospital length of stay including length of stay in critical care and hospital readmissions

This outcome was reported in one review (one trial, 65 participants) (Estcourt 2016b). In short-term RBC transfusion versus standard care, in people undergoing low- to medium-risk surgery, there may be little or no difference in the length of hospital stay, this evidence was low-quality according to GRADE criteria.

## DISCUSSION

### Summary of main results

We examined the evidence from published Cochrane Reviews for the use of RBC transfusions to treat or prevent complications in people with SCD. We included 15 reviews, however, in 10 of these reviews there was no RBC transfusion intervention (five reviews included other interventions and five reviews found no RCT evidence) (Figure 1). We concentrated this overview on the five reviews which include an RBC transfusion intervention comparison; however, one of these reviews included only 10 randomised participants and had no data to report (Dastgiri 2016). The four remaining reviews compared short- and long-term RBC transfusions to standard care; long-term RBC transfusions for preventing complications versus RBC transfusions to treat complications; restrictive versus liberal RBC transfusion strategy; and RBC transfusion versus disease-modifying agents (hydroxyurea). One review included trials in both adults and children, however, the majority of participants were children and adolescents; one review included pregnant women; and two reviews included trials in children and adolescents.

The key outcome findings of our review are as follows.

- In all four reviews and all comparisons there was little or no difference in the risk of death.

### ***Short-term RBC transfusion versus standard care***

- In people undergoing low- to medium-risk surgery, compared to standard care, RBC transfusions may decrease the risk of ACS in people with African haplotypes, but there was little or no difference in people with the Arabic haplotype. There was little or no difference in the risk of other SCD-related or transfusion-related complications.

### ***Long-term RBC transfusion versus standard care***

- In children and adolescents at high risk of stroke (abnormal TCDs or SCI), long-term RBC transfusions probably decrease the risk of stroke and may decrease the risk of ACS and painful crisis compared to standard care.
- Compared to standard care, long-term RBC transfusions may decrease the risk of SCI in children with abnormal TCD velocities, but there was little or no difference in the risk of SCI in children with normal TCD velocities and previous SCI.
- In children and adolescents already receiving long-term RBC transfusions for prevention of stroke, we do not know whether there is a difference in the risk of stroke between long-term RBC transfusion and standard care, but continuing long-term RBC transfusions may reduce the risk of SCI.
- In children with normal TCD velocities and SCI there was little or no difference in the risk of alloimmunisation or transfusions reactions between treatment groups, but RBC transfusions may increase the risk of iron overload.

### ***Long-term RBC transfusion versus RBC transfusion to treat complications***

- In pregnant women, long-term RBC transfusions may decrease the risk of painful crisis when compared to transfusions for complications; but there was little or no difference in the risk of other SCD-related complications or transfusion reactions.

### ***RBC transfusion versus disease-modifying agents (hydroxyurea)***

- For primary prevention of stroke in children, with abnormal TCD and no severe vasculopathy on MRI/MRA, who have received at least one year of RBC transfusions, we do not know whether there is a difference in the risk of stroke; SCI;

ACS; painful crisis; or iron overload when RBC transfusion is compared to disease-modifying agents (hydroxyurea).

- For secondary prevention of stroke in children and adolescents, we do not know whether there is a difference in the risk of stroke; SCI; ACS; or iron overload when RBC transfusion is compared to disease-modifying agents (hydroxyurea). However, hydroxyurea with phlebotomy may increase the risk of painful crisis and global SCD SAEs.

### ***Restrictive versus liberal RBC transfusion strategy***

- In people undergoing cholecystectomy, there was little or no difference in the risk of SCD-related or transfusion-related complications between transfusion strategies.

## **Overall completeness and applicability of evidence**

Although 15 reviews met the inclusion criteria, 10 of these reviews did not identify any trials with an RBC transfusion intervention, which demonstrates the striking lack of RCT evidence on the use of RBC transfusions to treat many SCD-related complications in both adults and children. Also SCD- and transfusion-related outcomes were often not measured or not reported in the trials which highlights the lack of evidence on overall effects of interventions on various disease and treatment outcomes. Both these issues are made transparent in a summary (Figure 1). There were few trials in the reviews and several of them were stopped early which could also affect the effect estimate of the interventions.

Some of the outcomes within the reviews were rare, such as death. This meant that because the reviews only contained a small number of participants the reviews would be unable to detect a difference in any rare outcome, even if one existed.

Few of the trials within the reviews included adults, however, the number of people with SCD are living longer, and over the past 40 years, the observed median survival has increased to over 60 years of age (Piel 2017). There is a pressing and ongoing need for effective therapies (including blood transfusions) to treat acute and chronic complications of SCD as the population ages. Moreover, the trials primarily included children or adolescents with HbSS disease with no evidence for effects in other SCD genotypes (HbS $\beta^0$ , HbSC or HbS $\beta^+$ ).

All of the reviews included trials that were conducted in high-income countries (USA, Canada, France and the UK). The potential risks associated with transfusion therapy are increased in low-income countries due to a lack of trained staff, modern equipment, sanitary conditions and clean, infection-free blood products (Ansong 2013; Ohene-Frempong 1999). Therefore, the risk-benefit ratio will be different in low-income countries and the results compiled in this overview may not be generalisable to that setting.



## Quality of the evidence

The quality of the included Cochrane Reviews was high based on AMSTAR criteria. The reviews were current, included comprehensive literature searches, reported the quality of outcomes using GRADE, and conclusions were appropriately based on the evidence.

However, the quality of the trials included in the reviews was variable as a result many outcomes were considered very low to low quality according to GRADE. One outcome was rated as having moderate-quality evidence of benefit (stroke in children and adolescents at high risk of stroke). The main sources of bias for individual outcomes in primary studies were lack of blinding and limitations in the methodological conduct of the trial (including: imbalance in baseline characteristics between treatment arms; cross-over between trial arms; quasi-randomisation; reporting outcomes as treated rather than intention-to-treat analysis), which led to the downgrading of the evidence. In two reviews, which included five trials (Estcourt 2017a; Estcourt 2017b), four trials were stopped early (Adams 1998; Adams 2005; Ware 2012; Ware 2016). Two were stopped for safety reasons (Adams 1998; Adams 2005); one for futility (for the composite primary end point of stroke and liver iron concentration, the increased risk of stroke with hydroxyurea was acceptable and within the non-inferiority stroke margin, hydroxyurea and phlebotomy was not superior to transfusion and chelation at reducing liver iron concentration) (Ware 2012); and one for non-inferiority (Ware 2016). Other sources of bias which led to the downgrading of evidence included risk of bias (e.g. baseline imbalance in the number of participants with severe vasculopathy (Ware 2012)) indirectness (most trials were only done in children); and imprecision as many of the outcomes had very wide CIs.

## Potential biases in the overview process

To our knowledge our overview process was free of bias; however, we only included Cochrane Reviews and there could be other non-Cochrane reviews which could impact on the findings of this overview. We undertook a thorough search of the *Cochrane Database of Systematic Reviews* and used Cochrane methods to select reviews, standard tools to assess the risk of bias and to extract data. We achieved consensus on any disagreements through discussion or by consulting a third overview author (SH). A potential bias in the overview process was that the authors of this overview were also authors of five included reviews (Estcourt 2016a; Estcourt 2016b; Estcourt 2017a; Estcourt 2017b; Roy 2017). The overview authors updated several reviews because they were out of date and did not provide GRADE assessments of the quality of the evidence (Estcourt 2016a; Estcourt 2016b; Estcourt 2017a). This made sure that this overview conformed to Ballard's proposed checklist for overviews (Ballard 2017).

## Agreements and disagreements with other studies or reviews

We identified two reviews that summarised evidence for RBC transfusions to treat complications of SCD (Expert Panel Report 2014; Josephson 2007). Yawn (Yawn 2014) summarises the Expert Panel Report from 2014 and makes a strong recommendation for the use of both hydroxyurea and RBC transfusion in many individuals with SCD (Expert Panel Report 2014). The report assesses evidence from both RCTs and observational studies. Yawn acknowledges the lack of high quality evidence for treating chronic SCD complications in particular (Yawn 2014). Josephson also reviews the evidence of RBC transfusion therapy to treat acute and chronic complications of SCD and acknowledges that many of the indications for RBC transfusion are based on anecdotal and observational studies (Josephson 2007). The number of included reviews in this overview which have no RBC transfusion intervention or RCT evidence, also highlights the overall lack of evidence to treat specific complications. It also highlights the missing data or lack of reporting of important patient outcomes of SCD-related SAEs and quality of life within trials, which makes it difficult to assess the benefit or harm of interventions. This overview provides the most current assessment of reviews of RCTs and includes two reviews that have assessed one of the largest and most recent trials in children with SCD (DeBaun 2014) which adds to the evidence base for the use of RBC transfusions in children and adolescents for stroke and SCI prevention.

## AUTHORS' CONCLUSIONS

### Implications for practice

This overview provides support from two high-quality Cochrane Reviews for the use of red blood cell (RBC) transfusions for preventing strokes in children and adolescents with sickle cell disease (SCD) at a high risk of stroke (abnormal transcranial dopplers (TCDs) or silent cerebral infarcts (SCI)) and evidence that it may decrease the risk of SCI in children with abnormal TCD velocities. In addition RBC transfusions may reduce the risk of acute chest syndrome and painful crisis in this population.

It also highlights the lack of high-quality evidence in adults with SCD and the number of reviews that have no evidence for the use of RBC transfusions across a spectrum of chronic SCD complications.

### Implications for research

This overview provides a concise summary of where high-quality evidence is lacking for the use of RBC transfusions to treat several SCD related-complications as evidenced by the number of reviews

with an RBC transfusion intervention or with no trials that met the reviews' inclusion criteria. Of particular concern is the lack of trials in adults with SCD given that people are living longer and may experience more of the chronic complications of SCD. Also of concern is the variable and often incomplete reporting of patient-relevant outcomes such as SCD-related serious adverse events and quality of life. Although it is acknowledged that recruitment to an RBC transfusion intervention in a trial is often slow and difficult, as the number of people in the population with chronic complications of SCD increases, it is an imperative to have a better understanding of the comparative benefits and harms of RBC transfusions and other interventions across the spectrum of SCD complications. Well-designed trials are also needed that report on patient-relevant outcomes as well as quality of life using validated scales in people receiving short- or long-term RBC transfusions. Two trials suggest that quality of life is improved with both short- and long-term RBC transfusion therapy and more robust measurements could provide data that may not only increase compliance with therapy but improve the lives of people living with SCD and facilitate recruitment to trials.

We also need to consider including non-randomised studies within future reviews to further assess adverse events (Zorzela 2016).

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- \* Indicates the major publication for the study

## ADDITIONAL TABLES

Table 1. Characteristics of reviews with an RBC transfusion intervention

Review (Included trials)	Objectives	Date assessed as up to date / Date of last search	Interventions	Comparison Interventions	Study Population Number of participants / type of SCD / age of participants	Number of included trials / study design / location of studies / duration of follow-up	Review outcomes for which data are reported	Review outcomes for which data are not reported
<a href="#">Estcourt 2017a</a> <b>Blood transfusion for preventing primary and secondary stroke in people with</b>	To determine whether chronic blood transfusion in people with SCD: 1. reduce occurrence of	04 April 2016 / 04 April 2016	<b>Chronic blood transfusion regimens to maintain HbS level &lt; 30% (+/- iron chelation)</b>	<b>Standard care</b>	N = 405 participants N = 130 children with abnormal TCD velocities and previous history	2 multicentre trials conducted in USA and Canada (STOP; STOP 2) Mean (SD) length of fol-	<b>Primary outcomes</b> · Incidence of clinical stroke · Mortality · Transfusion-related com-	Measures of organ damage

**Table 1. Characteristics of reviews with an RBC transfusion intervention** (Continued)

<p><b>sickle cell disease</b> (SIT (DeBaun 2014) ; STOP (Adams 1998) ; STOP2 (Adams 2005) ; SWITCH (Ware 2012) ; TWITCH (Ware 2016) )</p>	<p>stroke (primary prevention); 2. reduce recurrence of stroke (secondary prevention); 3. reduce mortality; 4. reduce other complications of SCD including pain crises, ACS and splenic sequestration; 5. are associated with unacceptable adverse events or costs.</p>				<p>of TIA or stroke (STOP) N= 79 children with normalised TCD velocities (STOP 2) N = 196 children with SCIs and normal TCD velocities (SIT) All 3 trials enrolled children with HbSS or Hb S<math>\beta^0</math> % with either 1 not clear majority HbSS <b>Mean (SD) age (years):</b> STOP: 8.3 (3.3); STOP 2: 8.6 (1.2); SIT: 8 (3).</p>	<p>low-up: transfusion arm: 21.0 (5.7) months; standard care: 18.3 (7.0) months (STOP) Median time from randomisation to an end-point event was 3.2 months (range, 2.1 to 10.1), and the mean (SD) was 4.5 (2.6) months (STOP 2) Both studies were stopped early due to safety concerns. 1 multicentre trial conducted in USA, Canada, France and UK (SIT) Children were followed for a median of 3 years.</p>	<p><b>Secondary outcomes</b> · Incidence of TIA · Haemoglobin level and haemoglobin S percentage · Measure of neurological impairment · Incidence of other sickle cell complications · QoL, inpatient stay, immobility and disability</p>	
			<p><b>Chronic blood transfusion regimens to maintain</b></p>	<p><b>Hydroxyurea with phlebotomy</b></p>	<p>N = 254 participants N = 133 history of stroke,</p>	<p>2 multicentre trials with 254 participants Conducted</p>	<p><b>Primary outcomes</b> · Mortality · Incidence of clinical</p>	<p>Measure of neurological impairment Incidence of</p>

Table 1. Characteristics of reviews with an RBC transfusion intervention (Continued)

			HbS level < 30% (+/- iron chelation)		chronic transfusion treatment and iron overload (SWITCH) N = 121 children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least 1 year of RBC transfusions (TWITCH) <b>HbSS:</b> SWITCH: transfusion: 100% hydroxyurea : 99% TWITCH: transfusion: 97% hydroxyurea: 100% <b>Mean (SD) age (years)</b> : SWITCH: transfusion: 13.3 (3.8); hydroxyurea: 13.0 (4.0) ; TWITCH: transfusion: 9.5 (0.68); hydroxyurea: 9.7 (3.2)	in USA and Canada Total duration of study treatment was: 30 months after randomisation, with a final study visit scheduled 6 months after discontinuation of study treatments (SWITCH) ; 24 months after randomisation with a 6-month visit after completing exit studies (TWITCH) Both studies were stopped early, 1 for futility (SWITCH) and 1 for non-inferiority (TWITCH)	stroke · Transfusion-related complications <b>Secondary outcomes</b> · Incidence of TIA or silent infarction · Haemoglobin level and haemoglobin S percentage	other SCD complications QoL Inpatient stay Immobil-ity and disability Measures of organ damage
<a href="#">Estcourt 2017b</a> <b>Inter-</b>	To assess the effectiveness of red blood	19 September 2016	<b>Chronic blood</b>	<b>Standard care</b>	N = 405 participants	2 multicentre trials	<b>Primary outcomes</b>	QoL and Cogni-



Table 1. Characteristics of reviews with an RBC transfusion intervention (Continued)

<p><b>ventions for preventing silent cerebral infarcts in people with sickle cell disease</b> (SIT (DeBaun 2014) ; STOP (Adams 1998) ; STOP2 (Adams 2005) ; SWITCH (Ware 2012) ; TWITCH (Ware 2016) )</p>	<p>transfusions and hydroxyurea alone or in combination and HSCT to reduce or prevent SCI in people with SCD</p>		<p><b>transfusion regimens to maintain HbS level &lt; 30% (+/- iron chelation)</b></p>		<p>N = 130 children with abnormal TCD velocities and previous history of TIA or stroke (STOP) N= 79 children with normalised TCD velocities (STOP 2) N = 196 children with SCI and normal TCD velocities (SIT) All 3 trials enrolled children with <b>HbSS or Hb S<math>\beta</math><sup>0</sup></b> % with either 1 not clear majority HbSS <b>Mean (SD) age (years)</b> : STOP: 8.3 (3.3); STOP 2: 8.6 (1.2); SIT: 8 (3).</p>	<p>conducted in USA and Canada (STOP, STOP 2) Mean (SD) length of follow-up: transfusion arm: 21.0 (5.7) months; Standard care: 18.3 (7.0) months (STOP) Median time from randomisation to an end-point event was 3.2 months (range, 2.1 to 10.1), and the mean (SD) was 4.5 (2.6) months (STOP 2) Both studies terminated early. 1 multicentre trial conducted in USA, Canada, France and UK (SIT) Children were followed for a median of</p>	<ul style="list-style-type: none"> <li>· Proportion of participants developing new or progressive SCI lesions on MRI</li> <li>· All-cause mortality</li> <li>· SAEs associated with different therapies or SCD</li> </ul> <p><b>Secondary outcomes</b></p> <ul style="list-style-type: none"> <li>· Clinical stroke (according to short-, medium-, and long-term outcomes)</li> <li>· Cognitive function as assessed by validated scales (such as Wechsler scales) from baseline and at various time intervals as reported in studies (at least 6 months)</li> <li>· QoL as assessed by validated scales (at least 6</li> </ul>	<p>tive function were not reported in STOP and STOP 2</p>
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Table 1. Characteristics of reviews with an RBC transfusion intervention (Continued)

						3 years.	months) · Any AEs associated with different therapies	
			<b>Chronic blood transfusion regimens to maintain HbS level &lt; 30% (+/- iron chelation)</b>	<b>Hydroxyurea with phlebotomy</b>	N = 254 participants N = 133 history of stroke, chronic transfusion treatment and iron overload (SWiTCH) N = 121 children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least 1 year of RBC transfusions (TWITCH) <b>HbSS:</b> SWITCH: transfusion: 100% hydroxyurea : 99% TWITCH: 97% transfusion: 97% hydroxyurea: 100% <b>Mean (SD) age (years)</b>	2 multicentre trials with 254 participants Conducted in USA and Canada Total duration of study treatment was: 30 months after randomisation, with a final study visit scheduled 6 months after discontinuation of study treatments (SWiTCH); 24 months after randomisation with a 6 month visit after completing exit studies (TWITCH) Both studies terminated early.	<b>Primary outcomes</b> · Proportion of participants developing new or progressive SCI lesions on MRI · All-cause mortality · SAEs associated with different therapies or SCD <b>Secondary outcomes</b> · Clinical stroke (according to short-, medium-, and long-term outcomes) · Any AEs associated with different therapies	Cognitive function as assessed by validated scales (such as Wechsler scales) from baseline and at various time intervals as reported in studies (at least 6 months) QoL as assessed by validated scales (at least 6 months) SWiTCH did not report any AEs

**Table 1. Characteristics of reviews with an RBC transfusion intervention** (Continued)

					: SWITCH: transfusion: 13.3 (3.8); hydrox- yurea: 13.0 (4.0) ; TWITCH: transfu- sion: 9.5 (2.68); hydrox- yurea: 9.7 (3.2)			
<a href="#">Estcourt 2016b</a> Preoper- blood trans- fusions for sickle cell disease ( <a href="#">Al-Jaouni 2006</a> ; <a href="#">Howard 2013</a> ; <a href="#">Vichinsky 1995</a> )	To determine whether there is ev- idence that preoperative blood trans- fusion in elective or emergency surgery: a. reduces mortality; b. re- duces com- plications directly re- lated to the surgical pro- cedure, such as local in- fection and bleeding; c. reduces seri- ous periop- erative com- plica- tions includ- ing pain, ACS and the postopera- tive fre- quency and severity of infections;	9 July 2015 / 17 March 2015	<b>Aggressive, designed to decrease the hae- moglobin S level to less than 30%</b>	<b>Conser- vative, de- signed to increase the haemo- globin level to 100 g/L</b>	N = 551 par- ticipants <b>HbSS:</b> 551 (100%) 75% aged < 20 years; 25% aged 20 years or older. Re- view reports on cholecys- tectomy (N = 230) and tonsillec- tomy/ ade- noidectomy (N = 107) subgroups only due to unit of anal- ysis is- sues with re- randomi- sation in the trial	1 par- allel RCT in USA 30-day fol- low-up	<b>Primary outcomes</b> · Periopera- tive mortal- ity (all- cause) · Serious complica- tions related to: § sickle cell disease § surgery § transfusion <b>Secondary outcomes</b> · Other transfusion- related com- plications · Haemoglo- bin level and haemo- globin S per- centage · Number of units or vol- ume (mL) of RBCs infused and, where known	· Length of stay · QoL · Mea- sures of or- gan damage



Table 1. Characteristics of reviews with an RBC transfusion intervention (Continued)

							<ul style="list-style-type: none"> <li>· QoL (reported in 1 trial only)</li> <li>· Haemoglobin level and haemoglobin S percentage (reported in 1 trial only)</li> <li>· Number of units or volume (mL) of RBCs infused and, where known for exchange transfusions (reported in 1 trial only)</li> </ul>	
Okusanya 2016	To assess the benefits and harms of a policy of prophylactic versus selective blood transfusion in pregnancy (Koshy 1988)	30 May 2016 / 30 May 2016	<b>Prophylactic transfusion: to optimise Hb concentration to a specified level</b>	<b>Selective (emergency) transfusion: when indicated by specific complication or a critically low level of Hb concentration</b>	N = 72 pregnant women with sickle cell anaemia (genotype HbSS) before 28 weeks of gestation	1 multi-centre study conducted in 6 secondary and university hospitals in the USA. Final evaluation conducted 6 weeks postpartum.	<b>Primary outcomes</b> <ul style="list-style-type: none"> <li>· Maternal death</li> <li>· Severe maternal morbidity (e.g. organ failure, pulmonary embolism, fat embolism, stroke, intensive care unit admission; or as defined by trial authors)</li> <li>· Perinatal death</li> </ul> <b>Secondary outcomes</b> <ul style="list-style-type: none"> <li><b>Mother</b> <ul style="list-style-type: none"> <li>· Sickle cell</li> </ul> </li> </ul>	<b>Mother</b> <ul style="list-style-type: none"> <li>· Iron overload</li> <li>· postpartum haemorrhage</li> <li>· Cumulative duration of hospital stay</li> </ul> <b>Infant</b> <ul style="list-style-type: none"> <li>· Admission to neonatal intensive care</li> <li>· Haemolytic disease of the newborn</li> </ul>

**Table 1. Characteristics of reviews with an RBC transfusion intervention** (Continued)

							crisis (due to vaso-occlusion, sequestration or · haemolysis) · Total units of blood transfused · Blood transfusion reaction	
<a href="#">Dastgiri 2016</a> <b>Blood transfusions for treating acute chest syndrome in people with Sickle cell disease</b> (PROACTIVE (Styles 2012))	To assess the effectiveness of blood transfusions, simple and exchange, for treating ACS by comparing improvement in symptoms and clinical outcomes against standard care	25 July 2016/ 25 April 2016	· Confirmed diagnosis of SCD: SS; SC; Sβ <sup>0</sup> ; Sβ <sup>+</sup> · Male or female · All ages · Any setting	· RBC transfusions (simple or exchange)	· Standard care	1 study met the inclusion criteria but no study results reported as out of 237 enrolled only 10 were randomised - the rest observational In the study publication they report 0/4 in transfusion arm no ACS and 2/6 in standard care arm with ACS	<b>Dastgiri 2016 Blood transfusions for treating ACS in people with SCD</b>	To assess the effectiveness of blood transfusions, simple and exchange, for treating ACS by comparing improvement in symptoms and clinical outcomes against standard care

ACS: acute chest syndrome

AEs: adverse events

Hb: haemoglobin

MRI/MRA: magnetic resonance imaging/magnetic resonance angiography

QoL: quality of life

RBC: red blood cell

SAEs: serious adverse events

SCD: sickle cell disease

SCI: silent cerebral infarcts

SD: standard deviation

TCD: transcranial doppler

TIA: transient ischaemic attack

**Table 2. Characteristics of reviews with other interventions**

Review (Included trials)	Objectives	Date assessed as up to date / Date of last search	Study Population Number of participants/ type of sickle cell/ age of participants	Interventions	Comparison Interventions	Number of included trials/ study design/location of studies/duration of follow-up
<a href="#">Roy 2017</a> <b>Interventions to treat chronic kidney disease in people with Sickle cell disease</b> (BABYHUG ( <a href="#">Wang 2011</a> ); <a href="#">Foucan 1998</a> )	To assess the effectiveness of any intervention in preventing or reducing kidney complications or CKD in people with SCD (including RBC transfusions, hydroxyurea and ACEi (either alone or in combination with each other)	/07 October 2026	People with all types of SCD of all ages and either gender	<ul style="list-style-type: none"> <li>• RBC transfusion</li> <li>• Hydroxyurea <ul style="list-style-type: none"> <li>• ACEi</li> <li>• In combination with each other</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Compared to each other</li> <li>• Placebo</li> <li>• Standard care</li> </ul>	Two studies met the inclusion criteria: one study compared hydroxyurea to placebo and the other study compared angiotensin converting enzyme inhibitors to placebo
<a href="#">Chinegwundoh 2004</a> Treatments for priapism in boys and men with sickle cell disease ( <a href="#">Serjeant 1985</a> )	To assess the benefits and risks of the different treatments for both stuttering and fulminant priapism in SCD	20 August 2010 / 22 July 2010	<ul style="list-style-type: none"> <li>• SCD: SS; SC; Sβ<sup>0</sup>; Sβ</li> <li>• Males</li> <li>• Priapism, fulminant or stuttering</li> <li>• All ages</li> <li>• Any race</li> <li>• Any ethnic origin</li> <li>• Any setting</li> </ul>	<ul style="list-style-type: none"> <li>• Any treatment for priapism in SCD</li> </ul>	<ul style="list-style-type: none"> <li>• Placebo;</li> <li>• No treatment;</li> <li>• Any other intervention</li> </ul>	One study comparing Stilboestrol 5 mg daily versus placebo.
<a href="#">Martí-Carvajal 2014</a> Interventions for treating leg ulcers in people with sickle cell disease ( <a href="#">Baum 1987</a> ; <a href="#">La Grenade 1993</a> ; <a href="#">McMahon 2010</a> ; <a href="#">Serjeant 1977</a> ; <a href="#">Serjeant 1997</a> ; <a href="#">Wethers</a>	To determine whether any clinical interventions (used either alone or in combination) are effective and safe when treating leg ulcers in people with SCD	21 October 2014 / 18 September 2014	<ul style="list-style-type: none"> <li>• Any SCD</li> <li>• Diagnosed with a leg ulcer</li> <li>• Treated in community, hospital or both</li> </ul>	<b>Systemic interventions</b> <ul style="list-style-type: none"> <li>• Vascular drugs</li> <li>• Antioxidant agents</li> <li>• Recombinant agents growth factors</li> </ul>	<ul style="list-style-type: none"> <li>• Conventional care</li> <li>• Another treatment regimen for leg ulcers in people with SCD</li> </ul>	Six studies met the review's inclusion criteria: Interventions included: <ul style="list-style-type: none"> <li>• Topical antibiotics</li> <li>• Solcoseryl® and Duo Derm</li> <li>• Arginine butyrate</li> </ul>

**Table 2. Characteristics of reviews with other interventions** (Continued)

1994)				<ul style="list-style-type: none"> <li>Pharmacologic stimulation of HbF synthesis <ul style="list-style-type: none"> <li>Oral zinc sulphate</li> </ul> </li> <li><b>Topical interventions</b> <ul style="list-style-type: none"> <li>Antibiotics and antiseptics</li> <li>Growth factors and related</li> <li>Steroids</li> <li>Dressing;</li> <li>Debriding agents;</li> </ul> </li> <li>Ccompression; miscellaneous (such as topical opioids)</li> <li><b>Non-pharmaceutical interventions</b></li> <li>Reconstructive surgery <ul style="list-style-type: none"> <li>Cell therapy</li> <li>Laser therapy</li> <li>miscellaneous</li> </ul> </li> <li>conventional care another treatment <ul style="list-style-type: none"> <li>regimen for leg ulcers in people with SCD</li> </ul> </li> </ul>		<ul style="list-style-type: none"> <li>Propionyl-L-carnitine</li> <li>RGD peptide matrix</li> </ul>
Martí-Carvajal 2016	To determine if the following treatments have any impact on avascular necrosis of bone in people with sickle cell disease (NOTSCA	3 July 2014 / 17 March 2014	<ul style="list-style-type: none"> <li>Confirmed diagnosis of SCD (trial included HbSS; SC; Sβ°)</li> <li>Any SCD -</li> </ul>	<b>Surgical treatment:</b> <ul style="list-style-type: none"> <li>Joint reconstruction (femoral head replacement, cup arthroplasty,</li> </ul>	<ul style="list-style-type: none"> <li>1 surgical approach compared to another, or to a non-surgical approach,</li> <li>2 non-</li> </ul>	One study: NOTSCA 2006 Randomised open-label Hip core decompression and physical therapy



**Table 2. Characteristics of reviews with other interventions** (Continued)

(Neumayr 2006)	short- and the long-term (efficacy, safety, and adverse events): any surgical versus non-surgical intervention, including combinations of surgical and non-surgical treatment. Also, address the following: 1. the role of decompression; 2. the relative effectiveness of surgical approaches (for studies comparing 2 surgical approaches); 3. types of prosthesis (glued or not, with or without bone grafts etc.)		related avascular necrosis • All ages • Male or female	articular surface replacement, total hip replacement); • Nucleus decompression; • Bone graft;  • Vascularized bone grafts; • Osteotomy <b>Non-surgical treatment:</b>  • Observation; • Analgesic drugs; • Electrical stimulation;  • Physiotherapy; • Resting of the joint; • RBC transfusion; • Stem cell transplant; • Treatment to prevent sickling;  • Bisphosphonates	surgical approaches compared	(N = 17) versus physical therapy alone (N = 21)
Oniyangi 2015 Phytomedicine (medicines derived from plants) for sickle cell disease (Akinsulie 2005; Wambebe 2001)	To assess the benefits and risks of phytomedicines in people with SCD of all types, of any age, in any setting	20 January 2015 / 26 March 2015	• People of all ages • SCD of any genotype in any geographic setting such as: homozygous (HbSS) and compound heterozygotes • Including SC disease (HbSC) and $\beta$ -thalassaemia (S $\beta$ 0/ • S $\beta$	• Administration (by any mode: topical; oral; or parenteral) of phytomedicines (defined as a remedy derived directly from plants or plant material and not synthesised).	• Placebo • Conventional treatment, including blood transfusion and hydroxyurea	Two studies met the inclusion criteria: one study compared Niprisan versus placebo or conventional treatment (blood transfusions not reported) The second study compared Ciklavit versus placebo or conventional

**Table 2. Characteristics of reviews with other interventions** (Continued)

			<ul style="list-style-type: none"> <li>• Proven by electrophoresis with family studies or DNA tests as appropriate</li> </ul>			treatment (blood transfusions not reported)
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ACEi: angiotensin-converting enzyme inhibitors

ACS: acute chest syndrome

CKD: chronic kidney disease

SCD: sickle cell disease

SD: standard deviation

TCD: transcranial doppler

TIA: transient ischaemic attack

**Table 3. Characteristics of reviews with no studies that met inclusion criteria**

Review	Objectives	Date assessed as up to date / Date of last search	Study Population Number of participants/ type of sickle cell/ age of participants	Interventions	Comparison Interventions
<a href="#">Estcourt 2016a</a> <b>Reg-ular long-term red blood cell transfusions for managing chronic chest complication in sickle cell disease</b>	Whether long-term blood transfusions show differences in the following: incidence of chronic chest complications; 'severity' or progression of established chronic chest complications; mortality associated with chronic chest complications; unacceptable adverse events	16 May 2016 / 25 April 2016	Any SCD: <ul style="list-style-type: none"> <li>• Confirmed diagnosis of SCD: SS; SC; S<math>\beta</math><math>\alpha</math>; S<math>\beta</math></li> <li>• Male or female</li> <li>• All ages</li> <li>• Positive or negative for a history of chronic or acute chest complications</li> </ul>	<ul style="list-style-type: none"> <li>• Regular RBC transfusions (simple top-up or exchange)</li> </ul>	<ul style="list-style-type: none"> <li>• Alternative treatment;</li> <li>• No treatment</li> </ul>
<a href="#">Martí-Carvajal 2009</a> <b>Inter-vention for treat-ing painful sickle cell crisis during</b>	To assess the effectiveness and safety of different regimens of packed red cell transfusion, oxygen	20 December 2009 / December 2007	<ul style="list-style-type: none"> <li>• Pregnant women with SCD (all types)</li> <li>• Any age</li> <li>• Excluded sickle cell trait</li> </ul>	<ul style="list-style-type: none"> <li>• RBC transfusion</li> <li>• Oxygen therapy</li> <li>• Fluid replacement</li> </ul>	<ul style="list-style-type: none"> <li>• Each other</li> <li>• Placebo</li> <li>• Standard care</li> </ul>

**Table 3. Characteristics of reviews with no studies that met inclusion criteria** (Continued)

<b>pregnancy</b>	therapy, fluid replacement therapy, analgesic drugs, and steroids for the treatment of painful sickle cell crisis during pregnancy			therapy <ul style="list-style-type: none"> <li>• Analgesia (nonsteroidal)</li> <li>• Anti-inflammatory agents or opiates agents)</li> <li>• Steroids (prednisone, dexamethasone, or methylprednisolone)</li> </ul>	
<a href="#">Martí-Carvajal 2015a</a> <b>Intervention for treating intrahepatic cholestasis in people with sickle cell disease</b>	To assess the benefits and harms of the interventions for treating intrahepatic cholestasis in people with SCD	13 March 2015 / 10 October 2014	<ul style="list-style-type: none"> <li>• SCD with intrahepatic cholestasis</li> <li>• Any age</li> <li>• Male or female</li> <li>• Hospital or community setting</li> </ul>	<ul style="list-style-type: none"> <li>• Simple RBC transfusion</li> <li>• Exchange transfusion</li> <li>• Liver transplant</li> <li>• Bile acid binding resins (cholestyramine colestipol)</li> <li>• Rifampin</li> <li>• Opiate antagonists (naltrexone, nalmefene)</li> <li>• Sertraline</li> <li>• Dexamethasone</li> <li>• Guar gum</li> <li>• Activated charcoal</li> </ul>	<ul style="list-style-type: none"> <li>• Conventional care</li> <li>• Each other</li> </ul>
<a href="#">Oringanje 2016</a> <b>Hematopoietic stem cell transplantation for people with sickle cell disease</b>	To determine whether stem cell transplantation can improve survival and prevent symptoms and complications associated with SCD. To examine the risks of stem cell transplantation against the potential long-term gain for people with SCD	31 March 2016 / 11 December 2015	<ul style="list-style-type: none"> <li>• Children and adults with SCD of all phenotypes, either gender and in all settings</li> </ul>	<ul style="list-style-type: none"> <li>• Methods of stem cell transplantation</li> </ul>	<ul style="list-style-type: none"> <li>• Methods of stem cell transplantation compared with each other</li> <li>• Supportive care (e.g. periodic transfusion, use of hydroxyurea,</li> <li>• Antibiotics, pain relievers, supplemental oxygen)</li> </ul>

**Table 3. Characteristics of reviews with no studies that met inclusion criteria** (Continued)

<a href="#">Owusu-Ofori 2015</a> <b>Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease</b>	To assess whether splenectomy (total or partial), to prevent acute splenic sequestration crises in people with SCD, improved survival and decreased morbidity in people with SCD, as compared with regular blood transfusions	15 July 2015 / 10 June 2015	Any SCD: <ul style="list-style-type: none"> <li>Confirmed diagnosis of SCD: SS; SC; Sβ<sup>o</sup>; Sβ</li> <li>Experienced at least one acute splenic sequestration crisis</li> </ul>	<ul style="list-style-type: none"> <li>Full or partial splenectomy</li> </ul>	<ul style="list-style-type: none"> <li>Conservative management</li> <li>No treatment</li> <li>Regimen of regular RBC transfusions (e.g. 4-weekly)</li> </ul>
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RBC: red blood cell

SCD: sickle cell disease

**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention**

AMSTAR Criteria <sup>1,2</sup>	<a href="#">Estcourt 2017a</a> <b>Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease</b>	<a href="#">Estcourt 2017b</a> <b>Interventions for preventing silent cerebral infarcts in people with sickle cell disease</b>	<a href="#">Estcourt 2016b</a> <b>Preoperative blood transfusions for sickle cell disease</b>	<a href="#">Okusanya 2016</a> <b>Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy</b>	<a href="#">Dastgiri 2016</a> <b>Blood transfusions for treating acute chest syndrome in people with sickle cell disease</b>
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<sup>1</sup> We applied a modified AMSTAR based on the univariable questions developed for the overview by Pollock 2014. See [Appendix 2](#) AMSTAR Checklist

<sup>2</sup> Modified AMSTAR answers are reported as: Y = yes; N = no; U = unsure; NA = not applicable

<b>1. Was an 'a priori' design provided</b>	<b>Y</b> Protocol available - objectives, participants, interventions and comparisons and primary and secondary outcomes clearly defined	<b>Y</b> Protocol available - objectives, participants, interventions and comparisons and primary and secondary outcomes clearly defined	<b>Y</b> Protocol available - objectives, participants, interventions and comparisons and primary and secondary outcomes clearly defined	<b>Y</b> Protocol available - objectives, participants, interventions and comparisons, and primary and secondary outcomes clearly defined	<b>Y</b> Protocol first published: Issue 2, 2009.
<b>2. Was there duplicate study selection and data extraction?</b>	<b>Y</b> Two independent review screened all electronically-derived citations and abstracts of papers identified in the search for	<b>Y</b> Two independent review authors screened all electronically-derived citations and abstracts of papers identified by the re-	<b>Y</b> Two independent review authors screened all electronically-derived citations and abstracts of papers identified by the re-	<b>Y</b> Two review authors independently assessed for inclusion all the potential studies identified as a result of	<b>Y</b> Two authors independently assessed the abstracts of trials identified from the searches. The two review authors inde-

**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention** (Continued)

	<p>relevance. We excluded trials that were clearly irrelevant at this stage based on a review of the abstract</p> <p>Two independent review authors formally assessed the full texts of all potentially-relevant trials for eligibility against the criteria outlined above. We resolved all disagreements by discussion without the need for a third review author</p> <p>Two review authors conducted the data extraction according to the guidelines proposed by Cochrane. We resolved disagreements between the review authors by consensus</p>	<p>view search strategy for relevance</p> <p>Two independent review authors (LE, PF) formally assessed the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We requested additional information from study authors as necessary</p> <p>The two review authors discussed the results of study selection and resolved our discrepancies</p> <p>Two review authors conducted the data extraction according to the guidelines proposed by the Cochrane Collaboration. Disagreements were resolved by consensus</p>	<p>view search strategy for relevance</p> <p>Two independent review authors (PF, LE) formally assessed the full texts of all potentially-relevant trials for eligibility against the criteria outlined above</p> <p>We resolved all disagreements by discussion without the need for a third review author</p> <p>Two review authors conducted the data extraction according to the guidelines proposed by the Cochrane Collaboration. Disagreements were resolved by consensus</p>	<p>the search strategy</p> <p>For eligible studies, both review authors independently extracted the data using the agreed form. We resolved discrepancies through discussion</p>	<p>pendently assessed the full text papers independently and resolved any disagreement on their eligibility for this review through discussion and consensus; or if necessary through a third party</p>
<p><b>3. Was a comprehensive literature search performed?</b></p>	<p><b>Y</b></p> <p>Searched Haemoglobinopathies Trials Register. We also searched the following databases for RCTs and SRs on April 4 2016: The Cochrane Library (CENTRAL &amp; DARE) - issue 4, 2016; issue 2, 2015 respectively MEDLINE (OvidSP, 1946 to April 4 2016) EMBASE (OvidSP, last 6 months to April 4 2016) CINAHL</p>	<p><b>Y</b></p> <p>Searched haemoglobinopathies trials register and the following databases for RCTs on 19 September 2016</p> <p>The Cochrane Library (CENTRAL, DARE, HTA, NHSEED) MEDLINE (OvidSP, Epub Ahead of Print, In-Process &amp; Other Non-Indexed Citations, Ovid MEDLINE Daily and</p>	<p><b>Y</b></p> <p>Searched haemoglobinopathies trials register and supplemented searches with a search of current MEDLINE, Embase, clinical trial registries, included mesh terms, key words and dates. Search strategies in appendix</p>	<p><b>Y</b></p> <p>The Cochrane Pregnancy and Childbirth Group's Trials Register which includes at least 2 major databases - and handsearches was searched 30 May 2016</p> <p>Provided Mesh terms but no key words. Trial registries were not searched</p>	<p><b>Y</b></p> <p>We conducted searches in the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND acute chest syndrome. We also searched the (<a href="http://www.ClinicalTrials.gov">www.ClinicalTrials.gov</a>) database to identify any additional relevant clinical studies and registered</p>

**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention** (Continued)

	(EB-SCOHost, to April 4 2016) PubMed (e publications only to April 4 2016) Transfusion Evidence Library (1950 to April 4 2016) LILACS (1982 to April 4 2016) IndMed (1986 to April 4 2016) KoreaMed (1997 to April 4 2016) Web of Science (Conference Proceedings Citation Index- Science (CPCI-S) -1990 to April 4 2016) We also searched the following trial databases for ongoing trials on 4 April 2016: ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (ICTRP)	Ovid MEDLINE, 1946 to 19 September 2016) PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Embase (OvidSP) CINAHL (EBSCOHost, 1937 to 19 September 2016) Transfusion Evidence Library (1950 to 19 September 2016) LILACS (1982 to 19 September 2016) Web of Science (Conference Proceedings Citation Index- Science (CPCI-S) - 1990 to 19 September 2016) We also searched the following trial databases for ongoing trials on 19 September 2016 ClinicalTrials.gov WHO International Clinical Trials Registry Platform (ICTRP).			clinical trials of the same topic. Regarding the relatively high prevalence of hereditary sickle cell disease (SS) and others associated disorders in south provinces of Iran (Zandian 2012), we tried to find any additional RCT studies registered in Iranian Registry of Clinical Trials ( <a href="http://www.irct.ir">www.irct.ir</a> ). Other databases and trial sites not search such as EMBASE and ICSTR
<b>4. Was the status of publication (i.e. grey literature) used as an Inclusion criterion?</b>	<b>Y</b> no limits on language or publication status.	<b>Y</b> Searches for unpublished work included in search of the Register. No language restrictions	<b>Y</b> Searches for unpublished work included in search of the Register. No language restrictions	<b>Y</b> Searches for unpublished work included in search of the Register. No language restrictions	<b>Y</b> We contacted the trial authors of the PROACTIVE trial for further data and information, but to date have received no
<b>5. Was a list of studies (included and excluded) provided?</b>	<b>Y</b> Includes study flow diagram.	<b>Y</b> Includes a flow diagram.	<b>Y</b> Includes a flow diagram.	<b>Y</b> Includes study flow diagram.	<b>N</b> No study flow diagram provided.

**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention** (Continued)

<b>6. Were the characteristics of the included studies provided?</b>	<b>Y</b> Detailed descriptions of participants interventions and outcomes of included studies provided	<b>Y</b> Detailed descriptions of participants interventions and outcomes of included studies provided	<b>Y</b> Detailed descriptions of participants interventions and outcomes of included studies provided	<b>Y</b> Detailed descriptions of participants interventions and outcomes of included studies provided	<b>Y</b> Detailed descriptions of participants interventions and outcomes provided
<b>7. Was the scientific quality of the Included studies assessed and documented?</b>	<b>Y</b> Assessed by two authors independently with Cochrane Risk of Bias tool, and Summary of findings table included and documented	<b>Y</b> Assessed by two authors independently with Cochrane Risk of Bias tool and Summary of findings table included and documented	<b>Y</b> Assessed by two authors independently with Cochrane Risk of Bias tool and Summary of findings table included and documented	<b>Y</b> Assessed by two authors independently with Cochrane Risk of Bias tool, and Summary of findings table included and documented	<b>Not applicable.</b>
<b>8. Was the scientific quality of the Included studies used appropriately in formulating conclusions?</b>	<b>Y</b> The quality of the evidence was very low to moderate across different outcomes according to GRADE methodology. This was due to the trials being at a high risk of bias due to lack of blinding, indirectness and imprecise outcome estimates. Due to lack of evidence this review cannot comment on management for adults with HbSS disease or children and adults with HbS $\beta^0$ , HbSC or HbS $\beta^+$ disease.	<b>Y</b> The quality of the evidence was very low to moderate across different outcomes according to GRADE methodology. This was due to: trials being at high risk of bias because they were unblinded; indirectness (the available evidence was for children with HbSS); and imprecise outcome estimates. There is low-quality evidence that long-term RBC transfusions may reduce the incidence of SCI in children with abnormal TCD velocities but have little or no effect on children with normal TCD velocities. In children who are at higher risk of stroke	<b>Y</b> Overall, the quality of the evidence was rated as low to very low across different outcomes according to GRADE methodology. This was due to two of the studies being at high or unclear risk of bias, and many of the outcome estimates being imprecise. Due to lack of evidence this review cannot comment on management for people with HbSC or HbS $\beta^+$ disease or patients with high baseline haemoglobin concentrations, or management of patients undergoing low risk surgery	<b>Y</b> Evidence from one small trial of very low quality suggests that prophylactic blood transfusion to pregnant women with sickle cell anaemia (HbSS) confers no clear clinical benefits when compared with selective transfusion. Currently, there is no evidence from randomised or quasi-randomised trials to provide reliable advice on the optimal blood transfusion policy for women with other variants of sickle cell disease (i.e. HbSC and HbS $\beta^+$ Thal). The available data and quality of evidence on this sub-	<b>Not applicable.</b>

**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention** (Continued)

		and have not had previous long-term transfusions, there is moderate-quality evidence that long-term RBC transfusions		ject are insufficient to advocate for a change in existing clinical practice and policy	
<b>9. Were the methods used to combine the findings of studies appropriate?</b>	<b>Y</b> Risk ratio reported and Peto odds ratio re-reported for outcomes with low event rates all confidence intervals included. Heterogeneity defined, There was no statistical heterogeneity, but if statistical heterogeneity was found to be above 75%, we would identify a reason for clinical heterogeneity and not perform a meta-analysis but comment instead on the results as a narrative	<b>Y</b> Risk ratio reported and Peto odds ratio re-reported for outcomes with low event rates all confidence intervals included. Heterogeneity defined, There was no statistical heterogeneity, but if statistical heterogeneity was found to be above 75%, we would identify a reason for clinical heterogeneity and not perform a meta-analysis but comment instead on the results as a narrative	<b>Y</b> Risk ratio reported and Peto odds ratio re-reported for outcomes with low event rates all confidence intervals included. Heterogeneity defined, identified and reported	<b>Y</b> For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals. No continuous data were analysed in this review. In future updates, if appropriate, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods	<b>Not applicable.</b>
<b>10. Was the likelihood of publication bias assessed?</b>	<b>Y</b> Mentioned that too few studies to assess publication bias.	<b>Y</b> Mentioned that too few studies to assess publication bias.	<b>Y</b> Mentioned that too few studies to assess publication bias.	<b>Y</b> Mentioned that too few studies to assess publication bias.	<b>Not applicable.</b>
<b>11. Was the conflict of interest stated?</b>	<b>Y</b> Lise Estcourt is partly funded by an NIHR Cochrane Programme Grant. Patricia Fortin is funded by an NIHR Cochrane Programme Grant. Sally Hopwell is partly funded by an NIHR	<b>Y</b> Lise Estcourt is partly funded by an NIHR Cochrane Programme Grant. Carolyn Doree: none to declare. Patricia Fortin is funded by an NIHR Cochrane Programme Grant. Sally Hop-	<b>Y</b> Lise Estcourt is partly funded by an NIHR Cochrane Programme Grant. Carolyn Doree: none to declare. Patricia Fortin is funded by an NIHR Cochrane Programme Grant. Sally Hop-	<b>Y</b> None known.	<b>Y</b> There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review



**Table 4. AMSTAR quality assessment: Reviews with an RBC transfusion intervention** (Continued)

	Programme Grant. Marialena Trivella is partly funded by an NIHR Programme Grant. Winfred Wang was a PI on several of the included trials	well is partly funded by an NIHR Programme Grant. Marialena Trivella is partly funded by an NIHR Programme Grant	well is partly funded by an NIHR Programme Grant. Marialena Trivella is partly funded by an NIHR Programme Grant		
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NIHR: National Institute for Health Research

PI: principal investigator

TCD: transcranial doppler

**Table 5. AMSTAR quality assessment: Reviews with other interventions**

AMSTAR Criteria <sup>1,2,3</sup>	Chinegwundoh 2004 Treatments for priapism in boys and men with sickle cell disease	Martí-Carvajal 2014 Interventions for treating leg ulcers in people with sickle cell disease	Martí-Carvajal 2016 Treatment for avascular necrosis of bone in people with sickle cell disease	Roy 2017 Interventions for chronic kidney disease in people with sickle cell disease	Oniyangi 2015 Phytomedicines (medicines derived from plants) for sickle cell disease
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<sup>1</sup> We applied a modified AMSTAR based on the univariable questions developed for the overview by Pollock 2014. See [Appendix 2](#) modified AMSTAR questions

<sup>2</sup> Modified AMSTAR answers are reported as: Y = yes; N = no; U = unsure; NA = not applicable

<sup>3</sup> Items 5 - 10 of AMSTAR were not assessed in the quality appraisal as the reviews did not include any studies with a red cell transfusion comparison

<b>1. Was an 'a priori' design provided</b>	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined
<b>2. Was there duplicate study selection and data extraction?</b>	<b>Y</b> Each author independently identified potentially relevant trials. Each author independently extracted data. No disagreement occurred, so no other expert in the field was invited	<b>Y</b> Two authors independently selected studies for inclusion, and extracted data. A third author was always included when two authors disagreed, all disagreements resolved by group discussion	<b>Y</b> The authors screened the search results for potentially relevant trials and independently assessed them. Each author used this form to extract data from each relevant study. We indepen-	<b>Y</b> Two independent review authors screened all citations and abstracts of papers identified by the search strategy for relevance. Two review authors independently and formally	<b>Y</b> Two authors (OO, DC) independently selected the trials for inclusion in the review using pre-defined inclusion criteria. two authors (NC, OO) had independently

**Table 5. AMSTAR quality assessment: Reviews with other interventions** (Continued)

	to make an independent assessment based on the selection criteria		dently extracted information from the papers	assessed the full texts of all potentially relevant trials for eligibility. Two review authors conducted the data extraction	extracted the data and resolved differences by referring to the original trial. The process was repeated for this update by both authors
<b>3. Was a comprehensive literature search performed?</b>	<b>Y</b> Studies identified in the Group's Haemoglobinopathies Trials Register. Searched Embase (1974 to 2003) ( <a href="#">Appendix 1</a> ) and the Internet (December 2003).	<b>Y</b> We identified relevant trials from the Group's Haemoglobinopathies Trials Register. Also searched LILACS and several other databases and websites	<b>U</b> Trials were identified from the Group's Haemoglobinopathies Trials Register. No Embase or trial registry search.	<b>Y</b> We identified trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register. In addition to this we searched the following databases for RCTs on 05 April 2016. CENTRAL, the Cochrane Library (current issue) MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, Embase CINAHL PubMed; Transfusion Evidence Library LILACS; IndMed; KoreaMed; PakMediNet; Web of Science; ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (ICTRP)	<b>Y</b> Relevant trials were identified from the Group's Haemoglobinopathies Trials Register. Relevant trials were also identified from the International Standard Randomised Controlled Trial Number Registry (ISCTN). An additional search of the Allied and Complementary Medicine (AMED) bibliographic database.
<b>4. Was the status of publication (i.e. grey literature) used as an Inclusion criterion?</b>	<b>Y</b> Attempts were also made to identify any unpublished trials through contact	<b>Y</b> We searched for trials, irrespective of publication status (trials	<b>U</b> Did not mention if any language restrictions. Stated that biblio-	<b>Y</b> We did not limit searches by language, year of publication or	<b>U</b> The bibliographic references of all retrieved trials and reviews were as-

**Table 5. AMSTAR quality assessment: Reviews with other interventions** (Continued)

	with experts in the field and personal communication with known authors.	may be unpublished or published as an article, an abstract, or a letter), language or country. No limit was applied with respect to the period of follow-up	graphic references of all retrieved literature were reviewed for additional reports of trials	publication type.	essed for additional reports of trials; lead authors were to be contacted if necessary No mention of limitation by language.
<b>11. Was the conflict of interest stated?</b>	<b>Y</b> None known.	<b>Y</b> In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials. In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'How to critically appraise clinical trials. Jennifer Knight-Madden and María José Martínez-Zapata: none known	<b>N</b> None known.	<b>Y</b> Noemi Roy: none known. Patricia Fortin: funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components Katherine Bull: none known. Carolyn Doree: none known. Sally Hopewell: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. Mari-alena Trivella: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components Lise Estcourt: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use	<b>Y</b> None known.

NIHR: National Institute for Health Research

**Table 6. AMSTAR quality assessment: Reviews with no studies identified**

<b>AMSTAR Criteria<sup>1,2,3</sup></b>	<a href="#">Estcourt 2016a</a> <b>Reg- ular long-term red blood cell transfu- sions for managing chronic chest com- plications in sickle cell disease</b>	<a href="#">Martí-Carvajal 2009</a> <b>Interven- tions for treating painful sickle cell crisis during preg- nancy</b>	<a href="#">Martí-Carvajal 2015a</a> <b>Interventions for treating intrahep- atic cholestasis in people with sickle cell disease</b>	<a href="#">Oringanje 2016</a> <b>Hematopoi- etic stem cell trans- plantation for peo- ple with sickle cell disease</b>	<a href="#">Owusu-Ofori 2015</a> <b>Splenec- tomy versus con- servative manage- ment for acute se- questra- tion crises in peo- ple with sickle cell disease</b>
<sup>1</sup> We applied a modified AMSTAR based on the univariable questions developed for the overview by Pollock 2014. See appendix xx modified AMSTAR questions					
<sup>2</sup> Modified AMSTAR answers are reported as: Y = yes; N = no; U = unsure; NA = not applicable					
<sup>3</sup> Items 5 - 10 of AMSTAR were not assessed in the quality appraisal as the reviews did not include any studies with a red cell transfusion comparison					
<b>1. Was an 'a priori' design provided</b>	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined	<b>Y</b> Protocol available - participants, interventions and comparisons and outcomes clearly defined
<b>2. Was there duplicate study selection and data extraction?</b>	<b>Y</b> Two review authors independently screened all the remaining references for relevance against the full eligibility criteria. We retrieved full-text articles for all references for which a decision on eligibility could not be made from title and abstract alone. The two review authors discussed the results of study selection and resolved any disagreements on trial inclusions by consensus	<b>Y</b> We planned to screen the results of our search strategy for potentially relevant trials, and independently assess them. We will independently extract the data	<b>Y</b> Two authors will screen the search results for potentially relevant trials and independently assess them. One author will extract data from the included trials using a spreadsheet data extraction form and one author will check the data entered	<b>Y</b> Two authors independently screened the ten trials found by the initial search of all the databases and reference lists to identify papers with potential relevance to the review. We obtained the full text of selected articles. Two authors independently selected trials for inclusion by applying the inclusion criteria to all potential trials.	<b>Y</b> We did not apply the process described below, as we were not able to identify any trials eligible for inclusion. However, if we include any trials in future updates of this review, we will apply the following methods. The two authors will independently identify potentially relevant trials from the results of the searches. Each author will independently extract data on trial information

**Table 6. AMSTAR quality assessment: Reviews with no studies identified** (Continued)

<b>3. Was a comprehensive literature search performed?</b>	<b>Y</b> Potentially relevant trials were identified from the Group's haemoglobinopathies Trials Register. We also searched for RCTs in the following databases: CENTRAL & DARE; MEDLINE; Embase; CINAHL; Pubmed; Transfusion Evidence Library; LILACS (BIREME/PAHO/WHO); KoreaMed; IndMed; PakMediNet; Web of Science; ClinicalTrials.gov; The WHO International Clinical Trials Registry (ICTRP); the ISRCTN Register EU Clinical Trials Register and the Hong Kong Clinical Trials Register	<b>Y</b> Searched the Cochrane Pregnancy and Childbirth Group's Trials Register. In addition, we searched using the terms using the terms sickle cell AND pregnancy: Cystic Fibrosis and Genetic Disorders Group's Trials Register (October 2007); LILACS database (1982 to Dec 5 2007); ClinicalTrials.gov <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>	<b>Y</b> Relevant studies from Disorders Group's Haemoglobinopathies Trials Register using the terms: Also searched LILACS; Epistemonikos; WHO International Clinical Trials Registry	<b>U</b> We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register. We searched the Meetings of the American society for Blood and Marrow Transplantation; Center for the International Blood and Marrow Transplant Research; and European Group for Blood and Marrow Transplantation. No additional databases or clinical trials sites searched.	<b>Y</b> Relevant trials were identified from Relevant trials were identified from the Group's Haemoglobinopathies Trials Register. In addition to the above, further subject specific electronic searched of MEDLINE and Embase
<b>4. Was the status of publication (i.e. grey literature) used as an Inclusion criterion?</b>	<b>Y</b> We did not limit searches by language or publication status.	<b>U</b> Did not mention if any language restrictions. Stated that bibliographic references of all retrieved literature were reviewed for additional reports of trials	<b>Y</b> We did not adopt any language or publication restrictions.	<b>U</b> All randomised controlled and quasi-randomised studies. Not stated if any language or publication status limitations	<b>Y</b> A comprehensive search strategy was formulated in an attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress)
<b>11. Was the conflict of interest stated?</b>	<b>Y</b> Lise Estcourt: partly funded by the NIHR Cochrane Programme Grant -	<b>N</b> None known.	<b>Y</b> In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-	<b>Y</b> Chioma Oringanje: none known. Eneida Nemecek: none known.	<b>Y</b> Dr Shirley Owusu-Ofori: none known. Tracey Remington: Man-

**Table 6. AMSTAR quality assessment: Reviews with no studies identified** (Continued)

	Safe and Appropriate Use of Blood Components Patricia Fortin: funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. Sally Hopewell: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. Mari-alena Trivella: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. Ian Hambleton: none declared Gavin Cho: none declared.		hour workshop on 'How to critically appraise clinical trials In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'How to critically appraise clinical trials Daniel Simancas-Racines: none known.	Oluseyi Oniyangi: none known.	aging Editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group
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NIHR: National Institute for Health Research

**Table 7. Mortality: Summary of findings**

Review	Intervention	Population	N Participants (N RCTs)	Relative effect estimate (95% confidence interval)	GRADE quality rating	Interpretation
<a href="#">Estcourt 2017a</a> <b>Pri- mary and sec- ondary stroke</b>	Long-term RBC transfusions versus standard care	Children with no previous long-term RBC transfusions (Follow-up 18 to 36 months)	326 (2 RCTs)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether long-term RBC transfusions decrease mortality
		Children and adolescents with previ-	79 (1 RCT)	Peto OR 8.0 (0.16 to 404.12)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether long-term RBC trans-

**Table 7. Mortality: Summary of findings** (Continued)

		ous long-term RBC transfusions (Follow-up 18 months)				fusions decrease mortality
	RBC transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least one year of RBC transfusions (6 months follow-up)	121 (1 RCT)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether hydroxyurea and phlebotomy decreases mortality
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and evidence of iron overload (6 months follow-up)	133 (1 RCT)	Peto OR 0.98 (0.06 to 15.92)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether hydroxyurea and phlebotomy decreases mortality
<a href="#">Estcourt 2017b</a> <b>Silent cerebral infarcts</b>	Long-term RBC transfusions versus standard care	Children or adolescents with abnormal TCD velocities 18 to 21 months follow-up	130 (1 RCT)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether long-term RBC transfusions decrease mortality
		Children or adolescents with normalised TCD velocities 18 months of follow-up	79 (1 RCT)	Peto OR 8.00 (0.16 to 404.12)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether long-term RBC transfusions decrease mortality

**Table 7. Mortality: Summary of findings** (Continued)

		Children with normal TCD velocities and silent stroke (median 3 years follow-up)	196 (1 RCT)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether long-term RBC transfusions decrease mortality
	RBC transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least one year of red cell transfusions (6 months follow-up)	121 (1 RCT)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether hydroxyurea and phlebotomy decreases mortality
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and evidence of iron overload (6 months follow-up)	133 (1 RCT)	Peto OR 1.02 (0.06 to 16.41)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether hydroxyurea with phlebotomy decreases mortality
<a href="#">Estcourt 2016b</a> <b>Pre-operative blood transfusions for sickle cell disease</b>	Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy	People with SCD undergoing cholecystectomy (Follow-up: 30 days)	230 (1 RCT) <sup>a</sup> cholecystectomy	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions decrease mortality



**Table 7. Mortality: Summary of findings** (Continued)

	Short-term RBC transfusion versus standard care	People with SCD undergoing low to medium risk surgery or any surgery other than cardiac surgery (Follow-up 30 days in one trial; not stated in 1 trial)	434 (2 RCTs)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether preoperative RBC transfusions decrease mortality
Okusanya 2016 Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy	Long-term RBC transfusions versus RBC transfusions to treat complications	Pregnant women with SCD (Follow-up for 21.5 to 24.5 weeks of prenatal care)	72 (1 RCT)	No deaths	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether prophylactic RBC transfusions decrease maternal mortality
		Perinatal mortality	72 (76 births) (1 RCT)	RR 2.85 (0.61 to 13.22)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether prophylactic RBC transfusions decrease perinatal mortality

<sup>1</sup> High Risk of bias in one or more domains using the Cochrane Risk of Bias tool

<sup>2</sup> Indirectness as specific population or procedure reported may not be generalisable to review question

<sup>3</sup> Imprecision as effect has wide confidence intervals and/or study has small number of people or low event rates

MRI/MRA: magnetic resonance imaging/magnetic resonance angiography

RBC: red blood cell

RCT: randomised controlled trial

SCD: sickle cell disease

TCD: transcranial doppler

**Table 8. SCD-related SAEs: Summary of findings**

GRADE summary of findings for SCD-related serious adverse events <sup>a</sup>								
Systematic Review	Interventions	Population (Follow-up)	N Participants (N RCTs)	Par- (N)	Reported outcomes and time points	Relative effect estimate (95% confidence interval)	GRADE quality rating	Interpretation

**Table 8. SCD-related SAEs: Summary of findings**

			326 (2 RCTs)	ACS	RR 0.24 (0.12 to 0.48)	⊕⊕○○ Low <sup>1,2</sup>	Long-term RBC transfusions may reduce the incidence of ACS
			326 (2 RCTs)	Painful crises	RR 0.62 (0.46 to 0.84)	⊕⊕○○ Low <sup>1,2</sup>	Long-term RBC transfusions may reduce the incidence of painful crisis
		Children and adolescents with previous long-term RBC transfusions (Follow-up 18 months)	79 (1 RCT)	Clinical stroke	RR 0.22 (0.01 to 4.35)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether continuing long-term red cell transfusions reduces the incidence of clinical stroke
			79 (1 RCT)	ACS	-	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
			79 (1 RCT)	Pain crisis	-	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
	RBC transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least one year of red cell transfusions (6 months follow-up)	121 (1 RCT)	Clinical stroke	No stroke occurred in either arm	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on the risk of stroke
			121 (1 RCT)	ACS	RR 2.03 (0.39 to 10.69)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hy-

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

							droxyurea and phlebotomy has any effect on ACS
			121 (1 RCT)	Pain crisis	RR 5.08 (0.61 to 42.23)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on pain crisis
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and ev-	133 (1 RCT)	Clinical stroke	RR 14.78 (0.86 to 253.66)	⊕○○○ Very low <sup>2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on the risk of stroke
			133 (1 RCT)	Global SCD SAEs	RR 3.10 (1.42 to 6.75)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may increase the risk of SCD related serious adverse events
			133 (1 RCT)	ACS	RR 0.33 (0.04 to 3.08)	⊕○○○ Very low <sup>1,2,3</sup>	Very uncertain whether switching to hydroxyurea and phlebotomy has any effect on the risk of ACS
			133 (1 RCT)	Pain crisis	RR 3.15 (1.23 to 8.11)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may in-

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

							crease the risk
			130 (1 RCT)	ACS	RR 0.30 (0.11 to 0.87)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may reduce the incidence of ACS
			130 (1 RCT)	Pain crisis	RR 0.90 (0.44 to 1.86)	⊕○○○ Very low <sup>1,2,3</sup>	Long-term RBC transfusions may be no different than standard care in reducing the incidence of pain crisis
		Children and adolescents with normalised TCD velocities (18 months follow-up)	77 (1 RCT)	New or progressive SCI lesions	RR 0.29 (0.09 to 0.97)	⊕⊕○○ Low <sup>1,2</sup>	Continuing RBC transfusions may reduce the incidence of SCIs
			79 (1 RCT)	ACS	-	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
			79 (1 RCT)	Pain crisis	-	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
		Children with normal TCD velocities and silent stroke (median 3 years follow-up)	196 (1 RCT)	New or progressive SCI lesions	RR 0.70 (0.23 to 2.13)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may be no different than standard care in reducing the incidence of SCIs
			196 (1 RCT)	Acute chest syndrome	RR 0.20 (0.08 to 0.51)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may reduce the incidence of ACS
			196 (1 RCT)	Pain crisis	RR 0.56 (0.40 to 0.78)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may re-

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

							duce the incidence of pain crisis
	RBC transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MR/MRA, who have received at least one year of red cell transfusions (6 months follow-up)	121 (1 RCT)	New or progressive SCI lesions	No SCIs occurred in either study arm	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on SCIs
			121 (1 RCT)	Global SCD SAEs	RR 1.52 (0.58 to 4.02)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know if switching to hydroxyurea and phlebotomy has any effect on total SAEs
			121 (1 RCT)	ACS	RR 2.03 (0.39 to 10.69)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on ACS
			121 (1 RCT)	Pain crisis	RR 5.08 (0.61 to 42.23)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on pain crisis
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and evidence of iron	133 (1 RCT)	New or progressive SCI lesions	Peto OR 7.28 (0.14 to 366.91)	⊕○○○ Very low <sup>2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on SCIs

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

		overload (6 months follow-up)					
			133 (1 RCT)	ACS	RR 0.33 (0.04 to 3.08)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether switching to hydroxyurea and phlebotomy has any effect on ACS
			133 (1 RCT)	Pain crisis	RR 3.15 (1.23 to 8.11)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may increase the risk of pain crisis
<b>Estcourt 2016b</b> <b>Preoperative blood transfusions</b>	Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy	People undergoing cholecystectomy (Follow-up: 30 days) (results for the tonsillectomy / adenoidectomy groups are similar)	230 (1)	Neurological complications	No events No effect estimate	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions reduce the risk of acute stroke
			230 (1)	ACS	RR 0.84 (0.38 to 1.84)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions reduce the risk of ACS
			230 (1)	Painful crises	RR 0.30 (0.09 to 1.04)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions reduce the risk of painful crisis
			230 (1)	Renal complications	No events No effect estimate	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

							RBC transfusions reduce the risk of renal complications
			230 (1)	Serious infection	RR 1.75 (0.59 to 5.18)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions reduce the risk of serious infection
	Short-term RBC transfusion versus standard care	People undergoing low-to medium-risk surgery or any surgery other than cardiac surgery (Follow-up 30 days in 1 trial; not stated in 1 trial)	434 (2)	Neurological complications	Peto OR 7.22 (1.24 to 41.94)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions increase the risk of neurological complications (no events in no preoperative transfusion group)
			65 (1)	ACS	RR 0.11 (0.01 to 0.80)	⊕⊕○○ Low <sup>1,3</sup>	Preoperative RBC transfusions may reduce the risk of ACS the population of African haplotypes
			369 (1) <sup>b</sup>		RR 4.81 (0.23 to 99.61)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions increase the risk of ACS (no events in control group) in the population of Arabic haplotypes

**Table 8. SCD-related SAEs: Summary of findings** (Continued)

			434 (2)	Painful crises	Peto OR 1.91 (0.61 to 6.04)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions reduce the risk of painful crisis
			65 (1)	Renal complications	No events No effect estimate	⊕⊕○○ Low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions reduce the risk of renal complications (no events)
			434 (2)	Serious infection	Peto OR 1.29 (0.29 to 5.71)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions reduce the risk of serious infection
<a href="#">Okusanya 2016</a> <b>Prophylactic vs selective blood transfusion</b>	Long-term RBC transfusions versus RBC transfusions to treat complications	Pregnant women with SCD (Follow-up for 21.5-24.5 weeks of prenatal care)	72 (1)	ACS	RR 0.67 (0.12 to 3.75)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether prophylactic RBC transfusions reduce the risk of ACS
			72 (1)	Painful crisis	RR 0.28 (0.12 to 0.67)	⊕⊕○○ Low <sup>1</sup>	Prophylactic RBC transfusions may reduce the risk of painful crisis
			72 (1)	Renal complications	RR 1.00 (0.07 to 15.38)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether prophylactic RBC transfusions reduce the risk of re-



**Table 8. SCD-related SAEs: Summary of findings** (Continued)

							nal complications
			72 (1)	Serious infection	RR 1.00 (0.07 to 15.38)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether prophylactic RBC transfusions reduce the risk of serious infection

<sup>a</sup> Sickle cell serious adverse events include: neurological, ophthalmological, respiratory, orthopaedic, vascular, hepatic or renal complications, vaso-occlusive pain crisis, priapism, infections

<sup>b</sup> Rated down by 2 for very serious risk of bias

<sup>1</sup> High Risk of bias in one or more domains using the Cochrane Risk of Bias tool

<sup>2</sup> Indirectness as specific population or procedure reported may not be generalisable to review question

<sup>3</sup> Imprecision as effect has wide confidence intervals and/or study has small number of people or low event rates

ACS: acute chest syndrome

MRI/MRA: magnetic resonance imaging/magnetic resonance angiography

OR: odds ratio

RBC: red blood cell

RCT: randomised controlled trial

RR: risk ratio

SAEs: serious adverse events

SCI: silent cerebral infarct

TCD: transcranial doppler

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings**

Table: Transfusion related adverse events (serious and non-serious) <sup>a</sup>								
Systematic Review	Intervention	Population (Follow-up)	N Participants (N RCTs)	Par- (N RCTs)	Reported outcomes and	Relative effect estimate (95% confidence interval)	GRADE quality rating	Interpretation
<a href="#">Estcourt 2017a</a> <b>Blood transfusion for preventing primary and secondary stroke in people with</b>	Long-term RBC transfusions versus standard care	Children with no previous long-term RBC transfusions (Follow-up 18 to 36 months)	121 (1 RCT)		Alloimmunisation	RR 3.16 (0.18 to 57.17)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know if long-term RBC transfusions increase the risk of alloimmunisation

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

sickle cell disease							
			121 (1 RCT)	Transfusion reactions	RR 5.17 (0.71 to 37.52)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know if long-term RBC transfusions increase the risk of transfusion reactions
			121 (1 RCT)	Iron overload (serum ferritin)	Increased in children receiving long-term RBC transfusions, incidence rate ratio 14.42 (5.41 to 875.17)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may increase the risk of iron overload
		Children and adolescents with previous long-term RBC transfusions (Follow-up 18	79 (1 RCT)	Alloimmunisation	1 participant who was in the continuing transfusion arm developed an alloimmunisation	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
			79 (1 RCT)	Transfusion reactions	7 participants in the continuing transfusion arm had 9 reactions to transfusions. 1 required hospitalisation	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
	RBC Transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA,	121 (1 RCT)	Liver iron concentrations	MD -1.80 (-5.16 to 1.56)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

		who have received at least one year of red cell transfusions (6 months follow-up)					
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and evidence of iron overload (6 months follow-up)	133 (1 RCT)	Liver iron concentrations	Hydroxyurea: 17.3 mg Fe/g dry weight iron, (IQR 10.0 to 30.6) ; transfusion: 17.3 mg Fe/g dry weight iron, (IQR 8.8 to 30)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations
<a href="#">Estcourt 2017b</a> <b>Interventions for preventing silent cerebral infarcts in people with sickle cell disease</b>	Long-term RBC transfusions versus standard care	Children or adolescents with abnormal TCD velocities (18 to 21 months follow-up)	130 (1 RCT)	Alloimmunisation	10 participants in the transfusion arm developed an alloimmunisation	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
			130 (1 RCT)	Transfusion reactions	12 participants in the transfusion arm had 16 mild reactions to blood products or transfusion procedures	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
			130 (1 RCT)	Iron overload	Iron overload developed faster than anticipated in children receiving transfusion, with mean (SD) serum fer-	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

				ritin rising to and 2509 μg/L (974 μg/L) at 24 months		
	Children and adolescents with normalised TCD velocities (18 months follow-up)	79 (1 RCT)	Alloimmunisation	1 participant who was in the continuing transfusion arm developed an alloimmunisation	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
		79 (1 RCT)	Transfusion reactions	7 participants in the continuing transfusion arm had 9 reactions to transfusions. 1 required hospitalisation	⊕○○○ Very low <sup>1,2,3</sup>	No comparative numbers reported
	Children with normal TCD velocities and silent stroke (median 3 years follow-up)	121 (1 RCT)	Alloimmunisation	RR 3.16 (0.18 to 57.17)	⊕○○○ Very Low <sup>1,2,3</sup>	We do not know if long-term RBC transfusions increase the risk of alloimmunisation
		121 (1 RCT)	Transfusion reactions	RR 5.17 (0.71 to 37.52)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know if long-term RBC transfusions increase the risk of transfusion reactions
		121 (1 RCT)	Iron overload (serum ferritin)	Increased in children receiving long-term RBC transfusions, incidence rate ratio 14.42 (5.41 to 875.17)	⊕⊕○○ Low <sup>2,3</sup>	Long-term RBC transfusions may increase the risk of iron overload

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

	RBC transfusion versus disease-modifying agents	Primary prevention Children with abnormal TCD velocities but no severe vasculopathy on MRI/MRA, who have received at least one year of red cell transfusions (6 months follow-up)	121 (1 RCT)	Liver iron concentrations	MD -1.80 (-5.16 to 1.56)	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations
		Secondary prevention Children and adolescents with previous stroke, at least 18 months of RBC transfusions, and evidence of iron overload (6 months follow-up)	133 (1 RCT)	Liver iron concentrations	Hydroxyurea: 17.3 mg Fe/g dry weight iron, IQR 10.0 to 30.6; transfusion: 17.3 mg Fe/g dry weight iron, IQR 8.8 to 30	⊕⊕○○ Low <sup>1,2</sup>	Switching to hydroxyurea and phlebotomy may have little or no effect on liver iron concentrations
<a href="#">Estcourt 2016b</a> <b>Preoperative blood transfusions for sickle cell disease</b>	Restrictive (to increase the total haemoglobin) versus liberal (to decrease the haemoglobin S level below a specified percentage) RBC transfusion strategy	People with SCD undergoing cholecystectomy (Follow-up: 30 days)	230 (1 RCT)	Alloimmunisation	RR 3.05 (1.14 to 8.20)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions increase the risk of alloim-
			230 (1 RCT)	Transfusion reactions	RR 2.18 (0.77 to 6.18)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfu-

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

							sions increase the risk of transfusion reactions
			230 (1 RCT)	Any transfusion complication	RR 1.85 (0.89 to 3.88)	⊕○○○ Very low <sup>1,2,3</sup>	We do not know whether aggressive RBC transfusions increase the risk of transfusion complications
	Short-term RBC transfusion versus standard care	People with SCD undergoing low to medium risk surgery or any surgery other than cardiac surgery (Follow-up for	434 (2) <sup>b</sup>	Serious transfusion complications	No events in 1 trial, circulatory overload reported in the preoperative transfusion group in 1 trial	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions increase the risk of serious transfusion complications
			65 (1) <sup>b</sup>	Alloimmunisation	Peto OR 7.17 (0.14 to 361.44)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions increase the risk of alloimmunisation
			434 (2)	Transfusion reactions	No events in 1 trial; 2 reactions reported in the preoperative transfusion group in 1 trial	⊕○○○ Very low <sup>1,3</sup>	We do not know whether preoperative RBC transfusions increase the risk of transfusion reactions
<a href="#">Okusanya 2016</a> <b>Prophylactic versus selective blood transfusion for sickle cell disease in</b>	Long-term RBC transfusions versus RBC transfusions to treat complications	Pregnant women with SCD (Follow-up for 21.5-24.5 weeks of prenatal care)	72 (1)	Transfusion reactions	RR 2.00 (0.54 to 7.39)	⊕○○○ Very low <sup>1,3</sup>	We do not know whether prophylactic RBC transfusions increase the risk of transfusion

**Table 9. Transfusion-related AEs (serious and non-serious): Summary of findings** (Continued)

pregnancy							reactions
<sup>a</sup> Serious and non-serious transfusion related adverse events can include: acute and delayed transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-associated dyspnoea, alloimmunisation, iron overload, problems of venous access)							
<sup>b</sup> Rated down by 1 for serious risk of bias and rated down by 2 for very serious risk of bias							
<sup>1</sup> High Risk of bias in one or more domains using the Cochrane Risk of Bias tool							
<sup>2</sup> Indirectness as specific population or procedure reported may not be generalisable to review question							
<sup>3</sup> Imprecision as effect has wide CIs and/or study has small number of people or low event rates							

CI: confidence interval

IQR: inter-quartile range

OR: odds ratio

MRI/MRA: magnetic resonance imaging/magnetic resonance angiography

RBC: red blood cell

RCT: randomised controlled trial

RR: risk ratio

SAEs: serious adverse events

SCD: sickle cell disease

TCD: transcranial doppler

## APPENDICES

### Appendix I. *The Cochrane Database of Systematic Reviews* search strategy

#1 MeSH descriptor: [Anemia, Sickle Cell] explode all trees

#2 (“h?emoglobin s” or “h?emoglobin sc” or “h?emoglobin se” or “h?emoglobin ss” or “h?emoglobin c” or “h?emoglobin d” or “Hb s” or “Hb sc” or “Hb se” or “Hb ss” or “Hb c” or “Hb d” or “sc disease\*”)

#3 (“sickle cell” or sicklemlia or sickled or sickling or meniscocyt\* or drepanocyt\*)

#4 #1 or #2 or #3

#5 MeSH descriptor: [Blood Transfusion] this term only

#6 MeSH descriptor: [Erythrocyte Transfusion] explode all trees

#7 ((blood or erythrocyte\* or “red cell\*” or “red blood cell\*” or RBC\*) near/5 (transfus\* or infus\* or unit\*))

#8 ((red cell\* or RBC\* or erythrocyte\* or red blood cell\* or whole blood or transfus\*) near/5 (use\* or usage\* or utiliz\* or utilis\* or requir\* or need\* or administ\* or replac\* or support\* or strateg\* or management or practic\* or indicat\* or criteri\* or standard\* or program\* or therapy)):ab

#9 ((red cell\* or RBC\* or erythrocyte\* or blood or transfus\*) and (use\* or usage\* or utiliz\* or utilis\* or requir\* or need\* or administ\* or replac\* or support\* or strateg\* or management or practic\* or indicat\* or criteri\* or standard\* or program\*)):ti

#10 (“allogeneic blood” or (unit\* near/2 blood) or “allogenic blood” or (blood near/2 exposure) or “donor blood” or “blood product\*” or “blood component\*” or “blood support”)

#11 hemotransfus\* or haemotransfus\* or hypertransfus\* or hemotherap\* or haemotherap\*

#12 (red cell\* or erythrocyte\* or blood or RBC\*) and transfus\*:ti

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Blood Component Transfusion] this term only

#15 MeSH descriptor: [Erythrocytes] this term only  
 #16 (red cell\* or red blood cell\* or erythrocyte\* or RBC\*)  
 #17 #14 and (#15 or #16)  
 #18 ((transfus\* or red cell\* or red blood cell\* or RBC\*) near/10 (trigger\* or thresh?old\* or target\* or restrict\* or liberal\* or aggressive\* or conservative\* or prophylactic\* or limit\* or protocol\* or policy or policies or practice\* or standard\*))  
 #19 (((transfus\* or red cell\* or red blood cell\* or RBC\* or h?ematocrit\*) and (level\* or critical\* or intensive\* or h?emorrhag\* or bleed\*)) or hypertransfus\*);ti  
 #20 #13 or #17 or #18 or #19  
 #21 #4 and #20

## Appendix 2. AMSTAR checklist

AMSTAR - a measurement tool to assess the methodological quality of systematic reviews.

### 1. Was an '*a priori*' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined or *a priori* published research objectives to score a 'yes'.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

### 2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: two people do study selection, two people do data extraction, consensus process or one person checks the other's work.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

### 3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, Embase, and MEDLINE). Key words or MESH terms (or both) must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least two sources + one supplementary strategy used, select 'yes' (Cochrane register/Central counts as two sources; a grey literature search counts as supplementary).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

### 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc.

Note: If review indicates that there was a search for 'grey literature' or 'unpublished literature', indicate 'yes'. SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey or unpublished literature.

- ☐ Yes
- ☐ No



☐ Can't answer

☐ Not applicable

5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided. Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select 'no'.

☐ Yes

☐ No

☐ Can't answer

☐ Not applicable

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

Note: Acceptable if not in table format as long as they are described as above.

☐ Yes

☐ No

☐ Can't answer

☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ('low' or 'high' is fine, as long as it is clear which studies scored 'low' and which scored 'high'; a summary score/range for all studies is not acceptable).

☐ Yes

☐ No

☐ Can't answer

☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating. Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies". Cannot score 'yes' for this question if scored 'no' for question 7.

☐ Yes

☐ No

☐ Can't answer

☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I<sup>2</sup>). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate 'yes' if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity or variability between interventions.

☐ Yes

- ☐ No
- ☐ Can't answer
- ☐ Not applicable

10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score 'no'. Score 'yes' if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a 'yes', must indicate source of funding or support for the systematic review AND for each of the included studies.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Shea et al. BMC Medical Research Methodology 2007 7:10 doi:10.1186/1471-2288-7-10

Additional notes (in italics) made by Michelle Weir, Julia Worswick, and Carolyn Wayne based on conversations with Bev Shea and/or Jeremy Grimshaw in June and October 2008 and July and September 2010.

## CONTRIBUTIONS OF AUTHORS

Patricia Fortin: overview content development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis.

Sally Hopewell: overview content development and methodological expert.

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

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## DECLARATIONS OF INTEREST

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## NOTES

### Serious adverse event

An adverse event is serious if it causes:

- death;
- is life-threatening;
- led to admission to hospital or prolongs inpatient stay;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect.