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Interventions for preventing silent cerebral infarcts in people with sickle cell disease (Protocol)

Estcourt LJ, Fortin PM, Hopewell S, Trivella M, Doree C, Abboud MR

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[Intervention Protocol]

Interventions for preventing silent cerebral infarcts in people with sickle cell disease

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of red blood transfusions and hydroxyurea alone or in combination and HSCT to reduce or prevent SCI in people with SCD.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a genetic haemoglobin disorder, which can cause severe pain, significant end-organ damage, pulmonary complications, and premature death (Chakravorty 2015). 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, South and Central America, the Caribbean, 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 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 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 (βS) 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 βS and βC alleles and tends to be a more moderate form of the disease. The third major type of SCD occurs when βS is inherited with a β-thalassaemia allele,

causing HbS/β-thalassaemia (Rees 2010). People who have inherited a thalassaemia null mutation (HbSß°) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbSβ+ thalassaemia have a milder disorder. In high-income countries, people with SCD are expected to live into their 40s, 50s 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).

In SCD under conditions of low oxygen levels, acidity and cellular dehydration, the HbS molecules polymerise and lead to membrane damage that distorts the red blood cells (RBCs) which take 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 the co-inheritance of genetic factors that affect the intracellular HbS or fetal haemoglobin concentration, e.g. the protective effects of co-inherited α-thalassaemia (Rumaney 2014; Steinberg 2012) or hereditary persistence of fetal haemoglobin (Akinsheye 2011; Steinberg 2012). Sickling of RBCs results in two main events: the 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). Reduced blood flow is mediated via a dynamic interaction between red cells containing sticky HbS, the vessel wall, and white cells (Rees 2010). Sickle 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 a reduced nitric oxide level within the blood; nitric oxide is sequestered by free haemoglobin (Hb), which over time favours endothelial dysfunction and the development of pulmonary hypertension (Kato 2006a; Kato 2006b).

The causes of cerebral infarcts in SCD are unclear and several of the mechanisms listed above may converge leading to vessel wall damage, and the narrowing and occlusion of cerebral blood vessels.

Silent cerebral infarcts

Silent cerebral infarcts (SCI) are the commonest neurological complication in children with sickle cell anaemia. These are defined as the presence of abnormalities on a magnetic resonance imaging (MRI) scan consistent with cerebral infarction (T-2 weighted and FLAIR imaging) without a clinical history or abnormalities on physical examination that are consistent with a previous stroke (DeBaun 2012). Some studies specify MRI lesions have to be at least 3 mm in diameter in children (Casella 2010), whereas in adults a more restrictive definition is sometimes used which includes a lesion measuring at least 5 mm on MRI (DeBaun 2012). The occurrence of SCI in children with SCD increases the risk for stroke, and new or enlarged SCIs. It also affects academic performance, increases cognitive deficits and may lower intelligence quotient (IQ) compared either to children with SCD who have normal MRI scans or with siblings without SCD (DeBaun 2012; DeBaun 2014).

The lack of longitudinal studies has made it difficult to define the natural history and prevalence of SCI in both children and adults. The 'Cooperative Study of Sickle Cell Disease' (CSSCD) cohort estimated a prevalence of 22% in children with HbSS aged six to 19 years; a French study reported a cumulative risk of SCI of 19% by eight years of age; 32% by 14 years of age; and 39% by 18 years of age (Bernaudin 2015; DeBaun 2016). In children in Kuwait, SCI is much more uncommon, with one study estimating a prevalence of only 3% (Adekile 2002). This may be explained by the fact that most people with SCD in the Arabian peninsula have persistently elevated Hb F levels, even as adults (Marouf 2003). It is still unclear as to when SCI first occurs in young children and if incidence rates change in adolescence (Bernaudin 2011; DeBaun 2012). Knowledge of the prevalence of SCI in adults with SCD is limited by the small number of studies and the small number of participants in studies, nevertheless it appears that up to one third of adults with SCD may develop SCI. Although more common in people with HbSS disease, SCI are also identified in people with HbSC disease (5% to 31%) and in people with HbSβ (3% to 38%) (DeBaun 2012). While SCI are uncommon in children in Kuwait, they are common in adults, with one study estimating a prevalence of 20% (Marouf 2003). These studies suggest no plateau in incidence and the resulting need for trials to study primary and secondary prevention (Bernaudin 2011; DeBaun 2012).

Relatively little is known about the causes of SCI and the optimal preventive therapy. However, the consistent finding that anaemia is strongly associated with SCI suggests that cerebral haemodynamic insufficiency (demand for oxygen exceeds supply) is a central component (DeBaun 2012). This is consistent with that fact that the majority of SCI are confined to deep white matter which suggests hypoperfusion or hypoxic events (Bernaudin 2015; van der Land 2016).

SCI may or may not be associated with increased transcranial doppler (TCD) velocities (tests that measure the speed of blood flow through the brain's blood vessels (either the internal carotid artery or the middle cerebral artery) by ultrasound). The TCD velocities are classed as normal (less than 170 cm per second); conditional (170 cm to less than 200 cm per second); or abnormal (at least 200 cm per second) (Adams 1998).

Risk factors for people with SCD developing SCI include lower haemoglobin levels, lower fetal haemoglobin, internal carotid artery stenosis, elevated systolic blood pressure (SBP) and a history of seizures (Bernaudin 2015; DeBaun 2012; van der Land 2016) .

In high-income countries randomised controlled trials (RCTs) (STOP, STOP II) have demonstrated that regular blood transfusion therapy (typically monthly) prevents strokes in children with SCD and high transcranial doppler (TCD) velocities (Abboud

2011; Adams 1998).

Description of the intervention

Red blood cell transfusions

Chronic RBC transfusions, either given as simple or exchange transfusions, form part of the management of a number of SCD complications such as the primary prevention of strokes in children with abnormal TCD velocities (Adam 2008) or the prevention of further chest crises in people with recurrent episodes (Howard 2015).

Children with elevated TCD velocities or previously elevated TCD velocities that have normalised developed fewer new SCI lesions with regular blood transfusions (Abboud 2011; Pegelow 2001).

In people with SCD, RBC transfusions have reduced sickle cell-related complications and improved quality of life, but are not without potentially serious complications. The benefits of transfusion therapy must be balanced against risks including infections, iron overload, acute or delayed haemolytic transfusion reactions, and increased complexity of compatibility testing (Chou 2013a; Chou 2013b; Porter 2013; Scheunemann 2010; Ubesie 2012).

Hydroxyurea (hydroxycarbamide)

Hydroxyurea has been in use since the 1980s and shown in clinical trials to be beneficial for SCD in reducing vaso-occlusive crises, chest crises and in improving survival (Field 2014). Hydroxyurea is currently the only approved therapeutic drug for the treatment of sickle cell anaemia (for adults with severe vaso-occlusive episodes of pain or acute chest syndrome) and its use has become widespread in both children and adults with SCD. Hydroxyurea significantly decreases haemolytic rate and improves the degree of baseline anaemia, which suggests that it could also decrease the rate of SCI (Bernaudin 2015).

Haematopoietic stem cell transplantation

Haematopoietic (blood forming) stem cell transplantation (HSCT) is the only known treatment for SCD that reduces or eliminates the sickling of RBCs. Allogeneic (from a relative (matched or mismatched) or matched unrelated donor) haematopoietic stem cells from bone marrow, peripheral blood, or umbilical cord blood are transplanted to produce partial or total correction of the sickle haemoglobin phenotype (Oringanje 2016). Risks are associated with both myeloablative conditioning (preparative regimen prior to the transplant) and the allogeneic stem cells. Risks include death, infertility and gonadal failure, development of secondary malignancies, graft versus host disease (GVHD) (an immune reaction of donor cells against recipient tissues), post-transplant immunological and neurological complications, and failure of the transplant (recurrence of SCD). HSCT has been used mostly in children under 16 years of age and there is limited evidence for its use in adults who may be at a higher risk of death (Oringanje 2016).

How the intervention might work

Red blood cell transfusion

The mechanisms for the reduction in stroke risk from chronic transfusion are not known (DeBaun 2006). However, a reduction in cells containing high amounts of HbS or an increase in Hb level could have beneficial effects on cerebral blood vessels or interactions between RBCs and endothelial cells (Adams 1998).

Children with the lowest baseline haemoglobin levels have higher odds of SCI than do those with the highest haemoglobin levels (DeBaun 2012). Also, an acute reduction in haemoglobin level (less than 55 g/L) is associated with an increase in new-onset SCIs, whether or not the child has SCD (Dowling 2012).

Transfusion does have an immediate haemodynamic effect measured by the reduction of middle cerebral artery velocity (Venketasubramania 1994).

The STOP trial has shown that RBC transfusions are effective for preventing stroke in children with elevated TCD velocities. It is also conceivable that RBC transfusions may prevent further SCI injury, even though the microvascular pathology of SCI is different from the involvement of the larger vessels (internal carotid and medium sized vessels) in stroke (DeBaun 2014).

Hydroxyurea

In preliminary studies hydroxyurea was substituted successfully for chronic transfusion for preventing secondary strokes. In a cohort study from 1992 to 2010, participants with severe baseline anaemia treated with hydroxyurea had a reduction in SCI from from 37.1% in a previous cohort (1988 to 2007) to 32.4% by age 14 years (Bernaudin 2015). Preliminary data from single-arm trials also suggest that hydroxyurea may be of benefit for the secondary prevention of SCI (Bernaudin 2011). Hydroxyurea is known to modestly increase the level of HbF via a range of mechanisms, including epigenetic modifications (Pule 2015). In RCTs on the use of hydroxyurea in SCD, it was found to increase total Hb and HbF levels and reduce vaso-occlusive crises; however, its benefit could not be solely attributed to the rise in HbF, with likely other mechanisms including effects on platelet count, white count, and red cell adhesion to endothelium (Charache 1995; Wang 2011). Hydroxyurea also decreases intravascular haemolysis which may ameliorate nitric oxide sequestration.

Haematopoietic stem cell transplantation

Allogeneic HSCT is the only curative treatment for SCD and a potential option for the primary or secondary prevention of SCI (Bernaudin 2007). In 36 HSCT transplant participants with a history of stroke, two had a recurrence post-transplantation, one participant experienced a transient ischaemic attack (TIA), and one had a severe cerebrovascular disorder with Moya-Moya disease and experienced fatal intracranial haemorrhage. After a median follow up of six years, the risk of stroke recurrence was 5.6%; however, no strokes or silent ischaemic lesions occurred in participants with successful engraftment (Bernaudin 2007). In a study carried out in the USA (eight participants with evidence of SCI before transplantation and who also had post-transplant studies) lesions were stable in three participants and four participants had lesions that decreased in size by brain MRI. There were no clinical strokes after transplantation in this group (Walters 2010).

In HSCT, high doses of chemotherapy are used to destroy an individual's own stem cells, which are then replaced with stem cells from a donor who is unaffected by SCD. The blood of transplant recipients contains normal red cells produced by the donated stem cells. Stem cell recipients typically need to take immunosuppressants for months to a few years. These medications can cause serious side effects.

Why it is important to do this review

SCI are the most common neurological injury in children and can occur in up to a third of adults with SCD. People with SCI have an increased risk for stroke and lower academic performance. There are no evidence-based strategies currently established for the primary prevention of SCI (DeBaun 2016). The effectiveness of either RBC transfusion, hydroxyurea or HSCT is unclear in secondary prevention of SCI. It is important for clinicians and people with SCD to understand what treatments are most effective based on the quality of evidence for both primary and secondary prevention in order to manage and reduce the serious sequelae of SCI.

OBJECTIVES

To assess the effectiveness of red blood transfusions and hydroxyurea alone or in combination and HSCT to reduce or prevent SCI in people with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Participants with homozygous SCD (SS), sickle beta thalassaemia (Sβ and Sβ+) and sickle haemoglobin C disease (SC) of all ages and both sexes, with or without evidence of SCI.

Types of interventions

1. RBC transfusions versus standard care
2. HSCT versus standard care
3. Hydroxyurea versus standard care or placebo
4. RBC transfusions versus HSCT
5. RBC transfusions versus hydroxyurea
6. Hydroxyurea versus HSCT
7. RBC transfusions combined with hydroxyurea versus standard care or hydroxyurea or RBC transfusions or HSCT alone

Types of outcome measures

Primary outcomes

1. Proportion of participants developing new or progressive SCI lesions on MRI
2. All-cause mortality
3. Serious adverse events (SAEs) associated with different therapies or SCD

We will categorise the proportion of participants developing new or progressive MRI lesions, all cause mortality, and SAEs according to short-, medium-, and long-term outcomes. We will report the exact definition of these time frames over time periods that are common to as many studies as possible (e.g. five years and under, six to 10 years, over 10 years).

Secondary outcomes

1. Clinical stroke (according to short, medium and long-term outcomes)
2. Cognitive decline as assessed by validated scales (such as Wechsler scales) from baseline and at various time intervals as reported in studies (at least six months)
3. Quality of life as assessed by validated scales (at least six months)
4. Any adverse events associated with different therapies

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND stroke.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

In addition to this we will search the following databases for RCTs.

- The Cochrane Library (CENTRAL, DARE, HTA, NHSEED) - current issue (www.cochranelibrary.com) (Appendix 1)
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to present) (Appendix 2)
- PubMed (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, for recent records not yet added to MEDLINE) (www.ncbi.nlm.nih.gov/sites/entrez) (Appendix 3)
- Embase (OvidSP, 1974 onwards) (Appendix 4)
- CINAHL (EBSCOHost, 1937 to present) (Appendix 5)
- Transfusion Evidence Library (1950 onwards) (www.transfusionevidencelibrary.com) (Appendix 6)
- LILACS (1982 onwards) (lilacs.bvsalud.org/en/) (Appendix 7)
- Web of Science (Conference Proceedings Citation Index-Science (CPCI-S) - 1990 to present) (Appendix 8).

We will also search the following trial databases for ongoing trials.

- ClinicalTrials.gov (clinicaltrials.gov/) (Appendix 9)
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) (Appendix 10)

We will combine searches in MEDLINE and Embase with RCT filters based on the recommended sensitivity-maximising Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011), and in CINAHL with an RCT filter based on the Scottish Intercollegiate Guidelines Network's (SIGN) RCT filter (www.sign.ac.uk/methodology/filters.html). We will not limit searches by language, year of publication or publication type.

Searching other resources

We will handsearch reference lists of included studies in order to identify further relevant studies. We will make contact with the lead authors of the included studies to identify any unpublished material, missing data or information regarding any ongoing studies.

Data collection and analysis

Selection of studies

We will select studies according to chapter seven of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; Higgins 2011b). Two review authors (LE, PF) will independently screen all electronically-derived citations and abstracts of papers identified by the search strategy for relevance. At this stage we will exclude studies that are clearly irrelevant based on the abstract. Two independent review authors (LE, PF) will formally assess the full texts of all potentially relevant trials for eligibility against the criteria outlined above. We will request additional information from study authors as necessary. The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, we will refer the decision of eligibility to a third review author (MA). We will report the results of study selection using a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two review authors (LE, PF) will conduct the data extraction according to Cochrane guidelines (Higgins 2011b). The review authors will try to come to a consensus; if an agreement cannot be reached, they will consult a third review author (MA). Authors will pilot data extraction forms on two included RCTs, thereafter two authors will extract data independently for all the studies.

Two authors (LE, PF) will independently extract outcome data using templates modified to reflect the outcomes in this review. The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. In addition we will use the available tables in Review Manager 5 (RevMan 2014) to extract data on study characteristics.

We will extract the following information for each study.

General information

Review author's name; date of data extraction; study ID; first author of study; author's contact address (if available); citation of paper; objectives of the study.

Study details

Study design; location, setting; sample size; power calculation; treatment allocation; inclusion and exclusion criteria; reasons for

exclusion; comparability of groups; length of follow up; stratification; stopping rules described; statistical analysis; results; conclusion; and funding.

Characteristics of participants

Age; gender; total number recruited; total number randomised; total number analysed; types of underlying disease; proportion of participants with lesions; TCD velocities; lost to follow-up numbers; dropouts (percentage in each arm) with reasons; protocol violations; previous treatments; current treatment; prognostic factors; haemoglobin S levels; SCD complications.

Interventions

Experimental and control interventions; method of red cell transfusion (simple, partial or full exchange transfusion); type of red cell transfusion (intermittent or chronic); dose and duration of hydroxycarbamide therapy; HSCT (relative, other donor, cord blood, bone marrow, peripheral blood, extent of HLA matching, preparative regimen); standard care.

Outcomes measured

Proportion of participants developing new or enlarged lesions; mortality (all cause); serious adverse events related to treatments or sickle lung disease; clinical stroke; cognitive decline; quality of life.

We will use both full-text versions and abstracts to extract data. We will use one data extraction form for each study for publications reporting on more than one study. We will extract data using one form only for studies reported in more than one publication. Where sources do not provide sufficient information, we will contact authors and study groups for additional details.

Assessment of risk of bias in included studies

We will perform an assessment of all RCTs using the Cochrane 'risk of bias' tool according to chapter eight of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). Two review authors (LE, PF) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We will report a brief description of the judgement statements upon which the authors have assessed potential bias in the 'Characteristics of Included Studies' table. We will ensure that a consensus on the degree of risk of bias is met through comparison of the review authors' statements and where necessary, through consultation with a third review author (MA). We will use Cochrane's tool for assessing the risk of bias, that will include the following domains.

- Selection bias (random sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective reporting)
- Other bias

Measures of treatment effect

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups. For dichotomous outcomes we will report the pooled risk ratio (RR) with a 95% confidence intervals (CI). Where the number of observed events is small (less than 5% of sample per group), and where studies have balanced treatment groups, we will report the Peto odds ratio (OR) with 95% CI (Deeks 2011).

For continuous outcomes we will record the mean, standard deviation (SD) and total number of participants in both the treatment and control groups. For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% CIs. If continuous outcomes are reported using different scales we will use standardised mean difference (SMD).

If available, we will extract and report hazard ratios (HRs) for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007).

Where appropriate, we will report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with CIs. If we cannot report the available data in any of the formats described above, we will perform a narrative report, and if appropriate we will present the data in tables.

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster randomised studies, cross-over studies, and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

If participants are randomised more than once we will contact the authors of the study to provide us with data on outcomes associated with the initial randomisation. For studies with multiple treatment groups we will only include subgroups that are considered relevant to the analysis. We will tabulate all subgroups in the 'Characteristics of Included Studies' section. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011d).

Dealing with missing data

Where data are identified to be missing or unclear in published literature, we will contact study authors directly. We will record

the number of participants lost to follow up for each study. Where possible, we will analyse data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per protocol analyses (Higgins 2011b).

Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess the statistical heterogeneity of treatment effects between studies using a Chi² test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if $I^2 > 50\%$, or considerable if $I^2 > 80\%$. We expect to identify at least moderate clinical and methodological heterogeneity within the included studies, and hence plan to use the random-effects model throughout. If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where we identify at least 10 studies for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Sterne 2011).

Data synthesis

We will perform analyses according to the recommendations of chapter nine of the *Cochrane Handbook for Systematic Reviews of Interventions* using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into the Review Manager 5 software (RevMan 2014). One review author will enter the data and a second will check for accuracy.

Where meta-analysis is feasible, we will use the random-effects model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and the inverse variance method (and SMDs as necessary) for continuous outcomes. If we identify heterogeneity over 80%, we will not perform a meta-analysis; rather we will report the results narratively within the results section of the review.

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses according to Cochrane recommendations for each of the following outcomes in order to assess the effect on heterogeneity (Deeks 2011).

1. Age of participant: neonate, child (one to 15 years), adult (16 years and older)
2. Genotype (homozygous sickle cell disease (SS), sickle beta thalassaemia (Sβ0 and Sβ+) and sickle haemoglobin C disease (SC))
3. TCD velocities (normal (less than 170 cm/s, conditional 170 to less than 200 cm/s, abnormal at least 200 cm/s)
4. Presence of previous SCI on MRI
5. Follow-up duration: longer-term RCTs (one year or longer) versus shorter term RCTs (less than one year)

Sensitivity analysis

We will assess the robustness of our findings by performing the following sensitivity analyses according to Cochrane recommendations where appropriate (Deeks 2011).

- Including only those studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).
- Including only those studies with less than a 20% dropout rate.

Summary of findings table

We will use the GRADE approach to create a 'Summary of findings' table, as suggested in chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will use the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low' using the five GRADE considerations below.

- Risk of bias: serious or very serious
- Inconsistency: serious or very serious
- Indirectness: serious or very serious
- Imprecision: serious or very serious
- Publication bias: likely or very likely

We will present the following outcomes within a summary of findings table for each intervention comparison.

- Proportion of participants developing new or progressive MRI lesions
- All-cause mortality
- Serious adverse events
- Clinical stroke
- Cognitive function
- Quality of life

We will use and specify time periods that are common to as many studies as possible (e.g. five years and under, six to 10 years, over 10 years).

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REFERENCES

Additional references

Abboud 2011
Abboud MR, Yim E, Mussallam KM, Adams RJ. Discontinuing prophylactic transfusions increases the risk of silent brain infarction in children with sickle cell disease: data from STOP II. *Blood* 2011;**118**(4):894–8.

Adam 2008
Adam S, Jonassaint J, Kruger H, Kail M, Orringer EP, Eckman JR, et al. Surgical and obstetric outcomes in adults with sickle cell disease. *American Journal of Medicine* 2008; **121**(10):916–21.

Adams 1998
Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *New England Journal of Medicine* 1998;**339**(1):5–11.

Adekile 2002
Adekile AD, Yacoub F, Gupta R, Sinan T, Haider MZ, Habeeb Y, et al. Silent brain infarcts are rare in Kuwaiti children with sickle cell disease and high Hb F. *Americal Journal of Hematology* 2002;**70**(3):228–31.

Akinsheye 2011
Akinsheye I, Alsultan A, Solovieff N, Ngo D, Baldwin CT, Sebastiani P, et al. Fetal hemoglobin in sickle cell anemia. *Blood* 2011;**118**(1):19–27.

Bernaudin 2007
Bernaudin F, Socie G, Kuentz M, Chevret S, Duval M, Bertrand Y, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood* 2007;**110**(7):2749–56.

Bernaudin 2011
Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Chevret S, Hau I, et al. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. *Blood* 2011;**117**:1130-40; quiz 1436.

Bernaudin 2015
Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Vasile M, Kasbi F, et al. Chronic and acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. *Blood* 2015;**125**(10):1653–61.

Casella 2010
Casella JF, King AA, Barton B, White DA, Noetzel MJ, Ichord RN, et al. Design of the silent cerebral infarct transfusion (SIT) trial. *Pediatric Hematology & Oncology* 2010;**27**(2):69–89.

Chakravorty 2015
Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. *Archives of Disease in Childhood* 2015;**100**(1):48–53.

Charache 1995
Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *New England Journal of Medicine* 1995;**332**(20):1317–22.

Chou 2013a
Chou ST. Transfusion therapy for sickle cell disease: a balancing act. *Hematology* 2013;**2013**:439–46.

Chou 2013b
Chou ST, Jackson T, Vege S, Smith-Whitley K, Friedman DF, Whesthoff CM. High prevalence of red blood cell alloimmunization in sickle cell disease despite transfusion from Rh-matched minority donors. *Blood* 2013;**122**(6): 1062–71.

DeBaun 2006
DeBaun MR, Derdeyn CP, McKinstry RC 3rd. Etiology of strokes in children with sickle cell anemia. *Mental Retardation & Developmental Disabilities Research Reviews* 2006;**12**(3):192–9.

DeBaun 2012
DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood* 2012;**119**(20):4587–96.

DeBaun 2014
DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *New England Journal of Medicine* 2014;**371**(8):699–710.

DeBaun 2016
DeBaun MR, Kirkham FJ. Central nervous system complications and management in sickle cell disease. *Blood* 2016;**127**(7):829–38.

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 9 Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Dowling 2012
Dowling MM, Quinn CT, Plumb P, Rogers ZR, Rollins NK, Koral K, et al. Acute silent cerebral ischemia and infarction during acute anemia in children with and without sickle cell disease. *Blood* 2012;**120**(19):3891–7.

Field 2014
Field JJ, Nathan DG. Advances in sickle cell therapies in the hydroxyurea era. *Molecular Medicine* 2014;**20 Suppl 1**: S37–42.

Frenette 2007
Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. *Journal of Clinical Investigation* 2007;**117**(4):850–8.

Gravitz 2014
Gravitz L, Pincock S. Sickle-cell disease. *Nature* 2014;**515** (7526):S1.

Grosse 2011
Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa. A neglected cause of early childhood mortality. *American Journal of Preventive Medicine* 2011;**41**(6 Suppl 4):S398–405.

Higgins 2011a
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011d
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Howard 2015
Howard J. Transfusion therapy in sickle cell disease. 25th Regional Congress of the International Society of Blood Transfusion in Conjunction with the 33rd Annual Conference of the British Blood Transfusion Society; 2015 Jun 27 - Jul 01; London, United Kingdom. 2015.

Kato 2006a
Kato GJ, McGowan V, Machado RF, Little JA, Taylor J, Morris CR, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood* 2006;**107**(6):2279–85.

Kato 2006b
Kato GJ, Hsieh M, Machado R, Taylor J 6th, Little J, Butman JA, et al. Cerebrovascular disease associated with sickle cell pulmonary hypertension. *American Journal of Hematology* 2006;**81**(7):503–10.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration..

Marouf 2003
Marouf R, Gupta R, Haider MZ, Adekile AD. Silent brain infarcts in adult Kuwaiti sickle cell disease patients. *American Journal of Hematology* 2003;**73**(4):240–3.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-Analyses: the PRISMA Statement. *Annals of Internal Medicine* 2009;**151**(4):264–9.

NICE 2010
National Institute for Health and Care Excellence (NICE). Sickle cell disease. http://cks.nice.org.uk/sickle-cell-disease. UK: NICE, 2010; Vol. (accessed 10 April 2016).

Oringanje 2016
Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD007001.pub4]

Parmar 1998
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Pegelow 2001
Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, et al. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. *Archives of Neurology* 2001;**58**(12):2017–21.

Piel 2012
Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin

in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2012;**381**(9861):142–51.

Pleasants 2014
Pleasants S. Epidemiology: a moving target. *Nature* 2014; **515**(7526):S2–3.

Porter 2013
Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. *ASH Education Program Book* 2013;**1**:447–56.

Pule 2015
Pule GD, Mowla S, Novitzky N, Wiysonge CS, Wonkam A. A systematic review of known mechanisms of hydroxyurea-induced fetal hemoglobin for treatment of sickle cell disease. *Expert Review of Hematology* 2015;**8**(5):669–79.

Rees 2010
Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010;**376**(9757):2018–31.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rumaney 2014
Rumaney MB, Ngo Bitoungui VJ, Vorster AA, Ramesar R, Kengne AP, Ngogang J, et al. The co-inheritance of alpha-thalassemia and sickle cell anemia Is associated with better hematological indices and lower consultations rate in Cameroonian patients and could improve their survival. *PLoS ONE* 2014;**9**:e100516.

Scheunemann 2010
Scheunemann LP, Ataga KI. Delayed hemolytic transfusion reaction in sickle cell disease. *American Journal of the Medical Sciences* 2010;**339**(3):266–9.

Schünemann 2011a
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sparkenbaugh 2013
Sparkenbaugh E, Pawlinski R. Interplay between coagulation and vascular inflammation in sickle cell disease. *British Journal of Haematology* 2013;**162**(1):3–14.

Steinberg 2012
Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. *American Journal of Hematology* 2012;**87**(8): 795–803.

Sterne 2011
Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook forSystematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; Vol. 8:16.

Ubesie 2012
Ubesie A, Emodi I, Ikefuna A, Ilechukwu G, Ilechukwu G. Prevalence of human immunodeficiency virus transmission among transfused children with sickle cell anemia in Enugu Nigeria. *Annals of Medical and Health Sciences Research* 2012;**2**(2):109–13.

van der Land 2016
van der Land V, Mutsaerts HJ, Engelen M, Heijboer H, Roest M, Hollestelle MJ, et al. Risk factor analysis of cerebral white matter hyperintensities in children with sickle cell disease. *British Journal of Haematology* 2016;**172**(2): 274–84.

Venketasubramania 1994
Venketasubramanian N, Prohovnik I, Hurlet A, Mohr JP, Piomelli S. Middle cerebral artery velocity changes during transfusion in sickle cell anemia. *Stroke* 1994;**25**(11): 2153–8.

Walters 2010
Walters MC, Hardy K, Edwards S, Adamkiewicz T, Barkovich J, Bernaudin F, et al. Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease. *Biology of Blood and Marrow Transplantation* 2010;**16**(2):263–72.

Wang 2011
Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011;**377**(9778):1663–72.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Anemia, Sickle Cell] explode all trees
#2 MeSH descriptor: [Hemoglobin, Sickle] explode all trees
#3 ("hemoglobin S" or "haemoglobin S" or "hemoglobin SC" or "haemoglobin SC" or "hemoglobin SE" or "haemoglobin SE" or "hemoglobin SS" or "haemoglobin SS" or "hemoglobin C disease" or "hemoglobin D disease" or "hemoglobin E disease" or "haemoglobin C disease" or "haemoglobin D disease" or "haemoglobin E disease" or "Hb SC" or HbSC or HbAS or HbSS or HbAC or "Hb SE" or "Hb SS" or "Hb C disease" or "Hb D disease" or "Hb E disease" or "SC disease" or "SC diseases")
#4 (sickle or sicklemia or sicklaemia or sickled or sickling or meniscocyt* or drepanocyt*)
#5 ((Hb S or HbS) near/3 (disease* or thalassemi* or thalassaemi*))
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Cerebral Infarction] explode all trees
#8 MeSH descriptor: [Brain Infarction] this term only
#9 MeSH descriptor: [Stroke] this term only
#10 MeSH descriptor: [Stroke, Lacunar] this term only
#11 ((ischemic or ischaemic or cerebrovascular) near/2 (event* or injur* or complication*))
#12 ((MRI or "magnetic resonance imaging" or neuroimaging or "white matter") near/3 abnormal*)
#13 (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*)
#14 ((cerebral or cerebellar or cerebrovascular or choroidal or hemispher* or cortical or subcortical or brain*) near/3 (infarct* or ischemi* or ischaemi* or stroke*))
#15 ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) near/5 (infarct* or ischemi* or ischaemi* or stroke*))
#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 #6 and #16

Appendix 2. MEDLINE (OvidSP) search strategy

1. exp Anemia, Sickle Cell/
2. Hemoglobin, Sickle/
3. (h?emoglobin S or h?emoglobin SC or h?emoglobin SE or h?emoglobin SS or h?emoglobin C disease or h?emoglobin D disease or h?emoglobin E disease or Hb SC or HbSC or HbAS or HbSS or HbAC or Hb SE or Hb SS or Hb C disease or Hb D disease or Hb E disease or SC disease*).tw,kf.
4. (sickle or sicklemia or sicklaemia or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf.
5. ((Hb S or HbS) adj3 (disease* or thalass?emi*)).tw,kf.
6. or/1-5
7. exp Cerebral Infarction/
8. Brain Infarction/
9. Stroke/
10. Stroke, Lacunar/
11. ((ischemic or ischaemic or cerebrovascular) adj2 (event* or injur* or complication*)).tw,kf.
12. ((MRI or magnetic resonance imaging or neuroimaging or white matter) adj3 abnormal*).tw,kf.
13. (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*).tw,kf.
14. ((cerebral or cerebellar or cerebrovascular or choroidal or hemispher* or cortical or subcortical or brain*) adj3 (infarct* or ischemi* or ischaemi* or stroke*)).tw,kf.
15. ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) adj5 (infarct* or ischemi* or ischaemi* or stroke*)).tw,kf.
16. or/7-15
17. 6 and 16

18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomi*.tw.
21. placebo.ab.
22. clinical trials as topic.sh.
23. randomly.ab.
24. groups.ab.
25. trial.tw.
26. or/18-25
27. exp animals/ not humans/
28. 26 not 27
29. 17 and 28

Appendix 3. PubMed search strategy

#1 ("hemoglobin S" OR "haemoglobin S" OR "hemoglobin SC" OR "haemoglobin SC" OR "hemoglobin SE" OR "haemoglobin SE" OR "hemoglobin SS" OR "haemoglobin SS" OR "hemoglobin C disease" OR "hemoglobin D disease" OR "hemoglobin E disease" OR "haemoglobin C disease" OR "haemoglobin D disease" OR "haemoglobin E disease" OR "Hb SC" OR HbSC OR HbAS OR HbSS OR HbAC OR "Hb SE" OR "Hb SS" OR "Hb C disease" OR "Hb D disease" OR "Hb E disease" OR "SC disease" OR "SC diseases" OR sickle* OR sickled OR sickling OR meniscocyt* OR drepanocyt*)
#2 (("Hb S" OR HbS OR sickl*) AND (disease* OR thalassemi* OR thalassaemi*))
#3 #1 OR #2
#4 ((ischemic or ischaemic or cerebrovascular) AND (event* or injur* or complication*))
#5 ((MRI or "magnetic resonance imaging" or neuroimaging or "white matter") AND abnormal*)
#6 (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*)
#7 ((cerebral or cerebellar or cerebrovascular or choroidal or hemispher* or cortical or subcortical or brain*) AND (infarct* or ischemi* or ischaemi* or stroke*))
#8 ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) AND (infarct* or ischemi* or ischaemi* or stroke*))
#9 #4 OR #5 OR #6 OR #7 OR #8
#10 ((random* OR blind* OR "control group" OR placebo* OR "controlled study" OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))
#11 #3 AND #9 AND #10

Appendix 4. Embase (OvidSP) search strategy

1. exp Sickle Cell Anemia/
2. Hemoglobin S/
3. (h?emoglobin S or h?emoglobin SC or h?emoglobin SE or h?emoglobin SS or h?emoglobin C disease or h?emoglobin D disease or h?emoglobin E disease or Hb SC or HbSC or HbAS or HbSS or HbAC or Hb SE or Hb SS or Hb C disease or Hb D disease or Hb E disease or SC disease*).tw.
4. (sickle or sicklemia or sickled or sickling or meniscocyt* or drepanocyt*).tw.
5. ((Hb S or HbS or sickl*) adj3 (disease* or thalass?emi*)).tw.
6. or/1-5
7. exp Cerebral Infarction/
8. exp Cerebrovascular Accident/
9. ((ischemic or ischaemic or cerebrovascular) adj2 (event* or injur* or complication*)).tw.
10. ((MRI or magnetic resonance imaging or neuroimaging or white matter) adj3 abnormal*).tw,kf.
11. (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*).tw.

12. ((cerebral or cerebellar or cerebrovascular or choroidal or hemispher* or cortical or subcortical or brain*) adj3 (infarct* or ischemi* or ischaemi* or stroke*)).tw.
13. ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) adj5 (infarct* or ischemi* or ischaemi* or stroke*)).tw.
14. or/7-13
15. 6 and 14
16. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
17. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.
18. 16 or 17
19. 15 and 18
20. limit 19 to embase

Appendix 5. CINAHL (EBSCOHost) search strategy

S1 (MH "Anemia, Sickle Cell+")
S2 TX ("hemoglobin S" or "haemoglobin S" or "hemoglobin SC" or "haemoglobin SC" or "hemoglobin SE" or "haemoglobin SE" or "hemoglobin SS" or "haemoglobin SS" or "hemoglobin C disease" or "hemoglobin D disease" or "hemoglobin E disease" or "haemoglobin C disease" or "haemoglobin D disease" or "haemoglobin E disease" or "Hb SC" or HbSC or HbAS or HbSS or HbAC or "Hb SE" or "Hb SS" or "Hb C disease" or "Hb D disease" or "Hb E disease" or "SC disease" or "SC diseases" or sickle or sicklemia or sicklaemia or sickled or sickling or meniscocyt* or drepanocyt*)
S3 TX ((Hb S or HbS or sickl*) N3 (disease* or thalass?emi*))
S4 S1 OR S2 OR S3
S5 (MH "Infarction")
S6 (MH "Cerebral Ischemia+")
S7 (MH "Stroke+")
S8 ((ischemic or ischaemic or cerebrovascular) N2 (event* or injur* or complication*))
S9 ((MRI or "magnetic resonance imaging" or neuroimaging or "white matter") N3 abnormal*)
S10 (cerebral vasculopath* or cerebrovascular accident* or cerebral vascular accident*)
S11 ((cerebral or cerebellar or cerebrovascular or choroidal or hemispher* or cortical or subcortical or brain*) N3 (infarct* or ischemi* or ischaemi* or stroke*))
S12 ((asymptomatic* or silent* or nonsymptomatic* or unsymptomatic* or non-symptomatic* or quiet* or symptomfree or symptom-free or symptomless or symptom-less or occult or "free of symptom" or "free of symptoms" or subclinical* or covert* or incomplete*) N5 (infarct* or ischemi* or ischaemi* or stroke*))
S13 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14 S4 AND S13
S15 (MH "Clinical Trials+")
S16 PT Clinical trial
S17 TX (clinic* N1 trial* OR controlled N1 trial*)
S18 TX ((singl* N1 blind*) or (singl* N1 mask*)) or TX ((doubl* N1 blind*) or (doubl* N1 mask*)) or TX ((tripl* N1 blind*) or (tripl* N1 mask*)) or TX ((trebl* N1 blind*) or (trebl* N1 mask*))
S19 TX (randomi* OR placebo*)
S20 (MH "Random Assignment")
S21 TX (random* N2 (allocat* OR assign*))
S22 (MH "Quantitative Studies")
S23 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
S24 S14 and S23

Appendix 6. Transfusion Evidence Library search strategy

sickle AND (cerebral OR ischemic OR ischaemic OR ischemia OR ischaemia OR cerebrovascular OR stroke OR infarct OR infarction OR MRI OR magnetic OR neuroimaging)

Appendix 7. LILACS search strategy

tw:(sickle) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 8. Web of Science CPCI-S search strategy

TOPIC: (sickle OR sickled OR sickling) *AND*
TOPIC: (ischemic OR ischaemic OR ischemia OR ischaemia OR stroke OR strokes OR infarct OR infarcts OR infarction OR hemispher* OR cerebral OR cerebrovascular OR subcortical OR cortical OR choroidal OR MRI OR magnetic OR neuroimaging) *AND*
TOPIC: (random OR randomly OR randomised OR randomized OR blind OR blinded OR control group OR placebo OR controlled study OR groups OR trial OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR pubmed OR cochrane OR embase)

Appendix 9. ClinicalTrials.gov search strategy

Search Terms: ischemic OR ischaemic OR ischemia OR ischaemia OR stroke OR strokes OR infarct OR infarcts OR infarction OR hemispheric OR cerebral OR cerebrovascular OR subcortical OR cortical OR choroidal OR MRI OR magnetic resonance imaging OR neuroimaging
Study Type: Interventional Studies
Condition: sickle

Appendix 10. WHO ICTRP search strategy

[Title: ischemic OR ischaemic OR ischemia OR ischaemia OR stroke OR strokes OR infarct OR infarcts OR infarction OR hemispheric OR cerebral OR cerebrovascular OR subcortical OR cortical OR choroidal OR MRI OR magnetic resonance imaging OR neuroimaging
Condition: sickle OR SCD
Recruitment Status: ALL]
OR
[Title: sickle OR SCD
Condition: ischemic OR ischaemic OR ischemia OR ischaemia OR stroke OR strokes OR infarct OR infarcts OR infarction OR hemispheric OR cerebral OR cerebrovascular OR subcortical OR cortical OR choroidal
Recruitment Status: ALL]
OR
[Title OR Condition: sickle OR SCD
Intervention: MRI OR magnetic resonance imaging OR neuroimaging
Recruitment Status: ALL]

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