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Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia (Protocol)

Fortin PM, Madgwick KV, Trivella M, Hopewell S, Doree C, Estcourt LJ

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[Intervention Protocol]

Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia

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ABSTRACT

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

To identify and assess the effectiveness of interventions to improve adherence to iron chelation therapy compared to standard care in people with SCD or thalassaemia including:

1. identifying and assessing the effectiveness of different types of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions);

2. identifying and assessing the effectiveness of interventions specific to different age groups (children, adolescents, adults).

BACKGROUND

Description of the condition

Haemoglobinopathies are a range of inherited disorders resulting from mutations of the globin genes (the protein component of haemoglobin). Two of the most common of these disorders are sickle cell disease (SCD) and thalassaemia.

Sickle cell disease

Sickle cell disease is an inheritable 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, kidney disease, and increased susceptibility to infections and stroke (Pleasants 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, Spanish-speaking regions in 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 mor-

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tality 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).

The term SCD refers to all mutations that cause the disease, of which there are three main types. 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) and is due to the co-inheritance of the βS and βC alleles; this 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 developed nations, 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). Red blood cell transfusions can be given to treat complications of SCD (e.g. acute chest syndrome), this often involves a single transfusion episode, or they can be part of a regular long-term transfusion programme to prevent complications of SCD such as stroke in children (Yawn 2014).

Thalassaemia

The term thalassaemia describes a group of inheritable disorders caused by the absence or reduction in globin chain production. This results in ineffective red blood cell production, anaemia and poor oxygen delivery. The genetic defect can be in the α or β globin chain (α-thalassaemia, β-thalassaemia or H disease). In β-thalassaemia, reduced or absent β globulin production leads to an excess of free α-globin chains resulting in severe anaemia and bone marrow hyperplasia (abnormal cell growth) preventing normal development. In H disease and α-thalassaemia, the α-globin chains are affected and disease can vary from mild (where reduced but adequate amounts of the functional globin chains are produced) to severe (where no effective haemoglobin is produced) (UK Thalassaemia Society 2008). Complications that may occur include infections, bone diseases, enlarged spleen, slowed growth rates, cardiomyopathy, venous thrombosis, pulmonary hypertension, and hypothyroidism (Rund 2005).

Thalassaemia is common in people from the Mediteranean, the Middle East, Southeast Asia, the Indian subcontinent, and Africa (Piel 2014; UK Thalassaemia Society 2008). It is estimated that there are over 1000 people with thalassaemia in the UK (APPG 2009). In high-income countries most affected children survive with a chronic disorder; however, most children born with thalassaemia are in low-income countries die before the age of five years (Modell 2008). Nevertheless, the thalassaemias are a global health burden due to population migration and growth and improved survival leading to an increase in the incidence of the disorder (Piel 2014).

Regular red blood cell transfusion is the standard treatment to correct anaemia and to enable growth and development, normal activities and to inhibit bone marrow expansion. People with severe forms, β-thalassaemia major, require life-long transfusions from the first year of life.

Iron chelation therapy and adherence

Regularly transfused people with SCD, as well as transfusion-dependent, and non-transfusion-dependent people with thalassaemia, are exposed to transfusion-related iron overload. Transfusion-related iron overload can lead to iron toxicity, with organs such as the heart, liver and endocrine glands being particularly vulnerable. Iron overload is the major cause of morbidity and mortality in thalassaemia (Aydinok 2014; Rund 2005, Trachtenberg 2012).

Iron chelating agents are used for preventing and treating iron overload. Deferoxamine (DFO) has been the standard treatment for the last 40 years; it is administered subcutaneously or intravenously usually over eight to 12 hours, up to seven days a week. More recently two oral chelating agents, deferiprone (DFP) and then deferasirox (DFX), have been licensed. These were initially introduced as second line agents in children six years and older with β-thalassaemia major, or in people when DFO is contraindicated or found to be inadequate (Fisher 2013). These oral agents are becoming more commonly used, particularly DFX, because of the ease of administration compared to subcutaneous or intravenous DFO (Aydinok 2014). The price of therapy varies depending on the formulation and the dose prescribed, but treatments can cost in excess of £1000 per month.

Licensed iron chelating agents are effective at iron removal; however, the treatment is not without side effects (Telfer 2006). Side effects with DFO include pain or skin reactions at the injection site, retinal toxicity and hearing loss. Side effects with DFX include skin rashes, gastroenteritis, increase in liver enzymes and reduced kidney function. Adverse events reported in people taking DFP include gastrointestinal disturbances, arthropathy (joint disease), raised liver enzymes, neutropenia (a decrease in neutrophils, a type of white blood cell, in the blood stream) and agranulocytosis (lowered white blood cell count). Regular blood sampling is recommended to monitor neutropenia, renal function and liver enzymes in people taking oral chelating agents (Fisher 2013).

Adherence to medications is defined as the extent to which a person's use of the medicine matches the agreed prescription from the healthcare provider (NICE 2009; Walsh 2014). Moderate adherence is defined as taking 60% to 80% of a prescribed dose, while high adherence can include the continued use of the medicine or

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taking at least 80% of the recommended dose. There are several ways to measure adherence including the self-reporting of medication use or more objective factors such as pill counts, prescription refills, urinary assays or in the case of iron chelation, signs of iron overload (Ryan 2014; Walsh 2014). Adherence rates can vary widely, a recent review reported that adherence rates to the iron chelator deferasirox ranged between 22% and 89% (Loiselle 2016).

Research suggests that iron chelation therapies impact on a person's quality of life and result in low levels of personal satisfaction. The intensive demands and uncomfortable side effects of iron chelation therapy can have a negative impact on daily activities and well-being, which may affect adherence to therapy (Abetz 2006; Payne 2008; Rofail 2010). Other factors affecting adherence to medications include inappropriate use, the quality of information provided to the individual, complex treatment regimens, as well as intolerance to the harms caused by the medications (Ryan 2014). Non-adherence can be both intentional and unintentional, with intentional non-adherence being influenced by such factors as poor communication, adverse effects, personal preferences or beliefs and disagreement with the need for treatment; whereas unintentional non-adherence is influenced by factors generally beyond the person's control such as forgetfulness or difficulties in understanding instructions (NICE 2009; Ryan 2014; Trachtenberg 2012). Sub-optimal adherence can increase adverse events associated with iron overload and result in increased cost of care, hospitalisations, and severe morbidity and mortality (Payne 2008; Vekeman 2016; WHO 2003).

Description of the intervention

The research on adherence and appropriate use of medicines is vast and complex and comprises a number of studies targeting people taking the medication, clinicians, indications and specific classes of medications. This research has also been reviewed in many systematic reviews as well as overviews of systematic reviews and in guidelines (Costello 2004; NCCPC 2009; NICE 2009; Ryan 2014; WHO 2003).

For this review we focus on the individual with SCD or thalassaemia, with interventions to increase adherence to iron chelation therapy being divided into three main categories. These are psychological and psychosocial interventions, educational interventions and medication interventions. These interventions may be delivered alone or in combination (as a complex intervention). For instance, combining psychological with psychosocial interventions such as symptom self management with peer support; or medication changes implemented with reconciliation strategies or complemented with medication information and education.

Psychological and psychosocial interventions

Psychological and psychosocial therapies that may promote medication adherence include interventions to promote behavioural change such as cognitive behavioural therapy (CBT), as well as peer support, counselling and skills development (communication, social, emotional). In addition there is an increasing emphasis on health-system interventions that may influence adherence such as patient-centred care and shared decision making (NCCPC 2009; Ryan 2014; WHO 2003).

In an outpatient clinic survey of 328 people with SCD using the Patient Health Questionnaire 9, up to 60% of people with SCD experienced mild to severe depressive symptoms. Interventions to address depression and other co-morbidities may promote medication adherence, and depending on the degree of depression or other co-morbidities can include medications, guided self-help, individual or group CBT or peer support (NCCMH 2010; NICE 2009; Thomas 2013).

Education interventions

Educational interventions may include disease and medication information, and assistance with communication skills to facilitate communication with healthcare providers (Haywood 2009; Ryan 2014). Interventions in the form of personal communication, structured presentations, and formal educational activities delivered by clinicians or non-medical personnel are included in this category.

Medication interventions

The identification and correction of medication issues such as under-utilisation, dosing and scheduling, allergies and contraindications, financial issues and inadequate monitoring may impact on adherence and health outcomes. Additional strategies such as positive medication changes to reduce burden or increase effectiveness, route of administration, risk minimisation and medication reconciliation may be used to promote improved medication adherence (NCCPC 2009; Ryan 2014).

How the intervention might work

Psychological and psychosocial interventions

People with chronic illness face a variety of psychological and psychosocial problems including depression, anxiety disorders, disease burden and restrictions on social and occupational functioning. Research suggests that skill development to help people with chronic illnesses cope with adverse effects of medication and any co-morbidities will decrease disease burden, and improve their health-related quality of life (NCCMH 2010; NCCPC 2009). The use of cognitive aids, clear instructions and realistic expectations can improve adherence (Wertheimer 2003). Person-centred

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psychological and psychosocial interventions encourage self-management skills, shared decision making and self-efficacy (NCCPC 2009; NICE 2009).

Educational interventions

Tailored educational interventions can be delivered to individuals or groups and can be delivered face-to-face or remotely. Educational interventions may include both a simple approach, such as evidence-based plain language information, by written or verbal communication, or a multi-faceted approach that considers the wider environment, management, decision making, life style and communication roles taken on by the person taking the medication (Ryan 2014). Each approach should be tailored to the individual (NCCPC 2009; WHO 2003).

Medication interventions

Iron levels are monitored in people receiving regular transfusions. An increasing iron burden may necessitate medication changes or more aggressive iron chelation therapy such as increasing doses or combination therapy. People may also change medications multiple times due to worsening iron overload, side effects, or personal preferences (Trachtenberg 2014). Medication changes that reflect personal preferences or minimize harms and improve outcomes, combined with medication reconciliation strategies including audit and feedback, prescription and medication helplines, counselling and age-appropriate discharge instructions, may help to address and improve adherence (NCCPC 2009; Ryan 2014).

Why it is important to do this review

Adherence to iron chelation therapy is necessary to decrease the risk of morbidity and mortality associated with iron overload. Poor adherence can also result in increased healthcare costs. It is therefore important to understand the effectiveness and limitations of interventions which can be used to influence adherence in people receiving iron chelation therapy for SCD or thalassaemia.

OBJECTIVES

To identify and assess the effectiveness of interventions to improve adherence to iron chelation therapy compared to standard care in people with SCD or thalassaemia including:

1. identifying and assessing the effectiveness of different types of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions);

2. identifying and assessing the effectiveness of interventions specific to different age groups (children, adolescents, adults).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing one or more adherence interventions, to standard care.

For studies comparing medications or medication changes, only RCTs will be considered.

For studies including psychological and psychosocial interventions, educational Interventions, or multi-component interventions, if no RCTs are available we will include non-RCTs (NRCTs), controlled before-after (CBA) studies, and interrupted time series (ITS) studies including repeated measures designs. We will use the Cochrane Effective Practice and Organisation of Care (EPOC) Group's definition of study designs to consider studies for inclusion (EPOC 2015)

We will include cluster-randomised trials, non-randomised cluster trials, and CBA studies if they have at least two intervention sites and two control sites. We will exclude cluster-randomised trials, non-randomised cluster trials, and CBA studies that have only one intervention or control site because the intervention (or comparison) will be confounded by study site making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables (EPOC 2015).

We will include ITS and repeated measures studies which have a clearly defined point in time when the intervention occurred and at least three data points before and after the intervention. We will exclude ITS studies that do not have a clearly defined point in time when the intervention occurred, fewer than three data points before and after the intervention, or the ITS study has ignored secular (trend) changes, performed a simple t-test of the pre- versus post-intervention periods and re-analysis of the data is not possible (in accordance with EPOC recommendations).

Types of participants

Children, adolescents, or their caregivers, and adults with SCD or transfusion-dependent or non-transfusion-dependent thalassaemia.

Types of interventions

- Psychological and psychosocial Interventions
- Educational Interventions
- Medication interventions
- Multi-component interventions (combining aspects of the above interventions)

versus

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- Standard care (as defined in the study)

Types of outcome measures

Primary outcomes

1. Adherence to iron chelation therapy rates (defined as per cent of doses administered (number of doses of the iron chelator taken, out of number prescribed), measured for a minimum of three months
2. Serious adverse events (SAEs) (including complications from the therapy, the disease itself, and non-adherence to chelation therapy)
3. All-cause mortality

We will categorise 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. zero to one year, one to five years, over five years)

Secondary outcomes

1. Sustained adherence to therapy (measured for a minimum of six months)
2. Health-related quality of life (as measured by validated instruments)
3. Iron overload (defined by ferritin over 1000 µg/L, or clinical symptoms, or signs of iron overload, e.g. magnetic resonance imaging (MRI) T2* cardiac iron content, MRI R2* liver iron content, liver biopsy, or the need for medically indicated additional or change in chelation therapy)
4. Organ damage (including cardiac failure, endocrine disease, surrogate markers of organ damage (creatinine), histologic evidence of hepatic fibrosis)
5. Other adverse events related to iron chelation

We will categorise health-related quality of life, iron overload and organ damage 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. up to six months, six to 12 months, over 12 months).

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 thalassaemia) AND iron chelation. The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (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 Cochrane Cystic Fibrosis and Genetic Disorders Group Module.

In addition to the above, we will conduct a broad search of the following databases to include RCTs, NRCTS CB and ITS studies.

- CENTRAL and DARE (the Cochrane Library, current issue) (www.cochranelibrary.com/)
- 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)
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to present)
- Embase (OvidSP, 1974 to present)
- CINAHL (EBSCOHost, 1937 to present)
- PsycInfo (EBSCOHost, 1900 to present)
- ProQuest Dissertations & Theses Global (ProQuest, 1861 to present)
- EBSCOHost Psychology and Behavioral Sciences Collection
- Web of Science Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 to current).

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

- ClinicalTrials.gov (clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)
- ISRCTN registry (www.isrctn.com/).

We will not limit the searches by language or publication date. Search strategies can be found in the appendix (Appendix 1).

Searching other resources

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

Data collection and analysis

Selection of studies

We will select studies according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

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Two review authors (PF, KM) will independently screen all electronically-derived citations and abstracts of papers identified by the search strategy for relevance. We will exclude studies that are clearly irrelevant at this stage based on the abstract. Two review authors (PF, KM) will independently formally assess the full texts of all potentially-relevant studies for eligibility against the criteria outlined above. We will resolve disagreements by discussion, if we do not reach a consensus, we will consult a third review author (LE). We will seek further information from study authors if the study or abstract contains insufficient data to make a decision about eligibility. We will design a study eligibility form which will include ascertaining whether the participants have SCD or thalassaemia, if the study addresses interventions to improve adherence to iron chelation therapy, and whether the study is randomised or a NRCT or a CBA or an ITS study. We will record the reasons why potentially-relevant studies failed to meet the eligibility criteria.

Data extraction and management

Two review authors (PF, KM) will extract the data according to the guidelines proposed by Cochrane (Higgins 2011a) and according to the criteria developed for non-randomised studies as recommended in Chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011). We will resolve disagreements by consensus. Data extraction forms will be piloted for RCTs, NRCTs or CBAs or ITS studies; thereafter, two authors (PF, KM) will extract data independently for all the studies using templates modified to reflect the outcomes in this review. In addition we will use the available tables in Review Manager 5 (RevMan 2014) to extract data on study characteristics as below.

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, loss to follow-up numbers, dropouts (percentage in each arm) with reasons, protocol violations, iron chelating agent, previous treatments, current treatment, prognostic factors, co-morbidities, ferritin levels.

Interventions

Details of the interventions including type of intervention whether psychological and psychosocial or educational or medication or multi-component interventions, how the intervention is being delivered (i.e. group, face-to-face, written information, electronically) and by whom (i.e. clinicians, peers) and where the intervention is being delivered (i.e. hospital, clinic, home).

Outcomes measured

All-cause mortality, SAEs, adherence rates, sustained adherence to therapy, health-related quality of life, iron overload defined by ferritin over 1000 µg/L or clinical symptoms or signs of iron overload or need for medically indicated additional or change in chelation therapy (or any combination of these), evidence of organ damage, other adverse events.

For non-RCTs, CBA or ITS studies we will also collect data, if available, on: confounding factors; the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in Chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

We will use both full-text versions and abstracts as data sources and use one data extraction form for each unique study. Where sources do not provide sufficient information, we will contact authors and study groups for additional details.

One review author will enter data and a second review author will check for accuracy.

Assessment of risk of bias in included studies

Two review authors (KM, PF) will assess all included studies for possible risks of bias as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c).

The assessment will include information about the design, the conduct and the analysis of the study. We will assess each criterion using Cochrane's tool for assessing the risk of bias for RCTs (classed as 'low', 'high' or 'unclear' risk) in the following areas.

- 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

We will use the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) to rate the quality of non-RCTs or CBA studies (Sterne 2016). The tool, uses signalling questions and covers seven domains (listed below) where the quality of evidence is rated as 'low', 'moderate', 'serious', 'critical' or 'no information'. Please refer to an appendix for a copy of the tool (Appendix 2).

- Bias due to confounding

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- Bias in the selection of participants
- Bias in measurement of interventions
- Bias due to departure from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in the selection of the reported result

For ITS studies we will use the risk of bias criteria below as suggested for EPOC reviews (EPOC 2015).

- Was the intervention independent of other changes?
- Was the shape of the intervention effect pre-specified?
- Was the intervention unlikely to affect data collection?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Was the study free from selective outcome reporting?
- Was the study free from other risks of bias?

We will resolve disagreements on the assessment of quality of an included study by discussion until we reach consensus or failing that by consulting a third review author.

Measures of treatment effect

RCTs

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

For dichotomous outcomes we will record the number of events and the total number of participants in both the treatment and control groups and report the pooled risk ratio (RR) with a 95% CI (Deeks 2011). 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).

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).

For cluster randomised studies we will extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice (MT) to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

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

Non-randomised studies

For dichotomous outcomes, if available we will extract and report the RR with a 95% CI from statistical analyses, adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post intervention / risk ratio pre intervention). For continuous variables, if available, we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models) or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups / the post-intervention level in the control group) (EPOC 2015).

ITS studies

For ITS studies that fulfil the criteria of analysis previously described, and from which relevant information can be extracted, we will standardise data by dividing the Level (or time Slope) and standard error (SE) by the SD of the pre-intervention slope, in order to obtain the effect sizes.

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

Given that we may include cluster randomised studies or non-randomised studies, and multiple observations for the same outcome in this review, we expect to encounter unit of analysis issues. Therefore, should we include any of these study designs in our review, we will treat these in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). For cluster designs, we will extract results adjusted for clustering, if analyses have not been adjusted for clustering, we will re-analyse the data taking clustering into account, if such an analysis is possible. If adjustment is not possible we will present data in a table.

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 two authors (KM, PF) will include subgroups that are considered relevant to the analysis. When appropriate, we will combine groups to create a single pair-wise comparison.

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If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011d).
We will deal with any unit of analysis issues arising from the inclusion of ITS studies according to the EPOC recommendations (EPOC 2015).

Dealing with missing data

Where we identify data as being missing or unclear in the 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 2011c).

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 analyse the data from RCTs, NRCTs, CBA and ITS studies separately.
We will assess statistical heterogeneity of treatment effects between studies using a Chi^2 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 is greater than 50%, or considerable if I^2 is greater than 75%. We anticipate that we will identify at least moderate clinical and methodological heterogeneity within the studies selected for inclusion; in such cases, we will use the random-effects model. 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

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of Cochrane (Deeks 2011). We will not conduct meta-analyses that include both RCTs and non-RCTs. We will use the random effects model for all analyses as we anticipate that true effects will be related but not the same for included studies. If we cannot perform a meta-analysis we will comment on the results as a narrative with the results from all studies presented in tables.

For RCTs where meta-analysis is feasible, we will use the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes, or outcomes that include data from cluster-RCTs. If heterogeneity is found to be above 75%, and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity then we will not perform a meta-analysis.
If meta-analysis is feasible for non-RCTs or CBA studies we will analyse these separately. We will only analyse outcomes with adjusted effect estimates if these are adjusted for the same factors using the inverse variance method as recommended in Chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).
If meta-analysis is feasible for ITS studies, we will use the effect sizes (if reported in the included studies or obtained (as described earlier)) and pool them using the generic inverse variance method in RevMan (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses according to Cochrane's recommendations (Deeks 2011) for each of the following criteria, and separately for the different study design types included in the review in order to assess the effect on heterogeneity.

- Age of participant (child (one to 12 years), adolescent (13 to 17 years) adult (18+ years))
- Type of disease (SCD or thalassaemia)
- Route of administration of iron chelating agents (oral, intravenous or subcutaneous)

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
- Duration of follow-up (up to and including six months compared to over six months)

Summary of findings table

We will use the GRADE approach to generate a 'Summary of Findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a). 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.

- Risk of Bias (serious or very serious)

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- Inconsistency (serious or very serious)
- Indirectness (serious or very serious)
- Imprecision (serious or very serious)
- Publication bias (likely or very likely)

For non-RCTs or CBA or ITS studies, we will also consider the following factors.

- Dose response (yes or no)
- Size of effect (large or very large)
- Confounding either reduces the demonstrated effect or increases the effect if no effect was observed (yes or no)

In GRADE non-RCTs or CBA or ITS studies will be rated initially as low quality and upgraded according to GRADE guidelines if appropriate. We will present outcomes for these studies in separate tables from outcomes for the results of RCTs.
We will report the following outcomes in each 'Summary of findings' table.

1. All-cause mortality (most common time frame used in most studies)
2. Serious adverse events (most common time frame used in most studies)
3. Adherence rates (minimum of three months)
4. Sustained adherence (six months or more)
5. Quality of life (most common time frame used in most studies)

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

The following databases will be searched using the strategies below (without study filters):

CENTRAL, the Cochrane Library

#1 MeSH descriptor: [Patient Acceptance of Health Care] explode all trees

#2 MeSH descriptor: [Patient Education as Topic] this term only

#3 MeSH descriptor: [Data Collection] explode all trees

#4 (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*):ti

#5 ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satis-

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faction or dissatisfaction or persist* or educat* or questionnaire*) near/6 (patient* or treatment* or therapy or therapies or medication* or drug*)):ab
#6 (patient* near/3 (dropout* or drop* out*))
#7 MeSH descriptor: [Treatment Refusal] this term only
#8 (treatment* near/3 refus*)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Iron Chelating Agents] explode all trees
#11 MeSH descriptor: [Chelation Therapy] this term only
#12 (chelat* near/3 (treatment* or therap*))
#13 (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom)
#14 (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp)
#15 (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670")
#16 (iron near/5 (chelat* or reduc*))
#17 #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 MeSH descriptor: [Thalassemia] explode all trees
#19 (thalassemi* or thalassaemi* or lepore or hydrops fetalis)
#20 ((hemoglobin or haemoglobin) near/3 disease)
#21 (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis)
#22 ((mediterranean or erythroblastic or cooley*) next (anemi* or anaemi*))
#23 MeSH descriptor: [Iron Overload] explode all trees
#24 (iron near/3 (overload* or over-load*))
#25 MeSH descriptor: [Hemoglobinopathies] this term only
#26 MeSH descriptor: [Hemoglobin C Disease] this term only
#27 (hemoglobinopath* or haemoglobinopath*)
#28 MeSH descriptor: [Anemia, Sickle Cell] explode all trees
#29 (barts and (blood or plasma))
#30 (sickle cell or sicklemi* or sickled or sickling or meniscocyt* or drepanocyt*)
#31 (hemoglobin S or hemoglobin SC or hemoglobin SE or hemoglobin SS or hemoglobin C or hemoglobin D or haemoglobin S or haemoglobin SC or haemoglobin SE or haemoglobin SS or haemoglobin C or haemoglobin D Hb S or Hb SC or Hb SE or Hb SS or Hb C or Hb D or SC disease)
#32 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
#33 #9 and #17 and #32
#34 ((thalassemi* or thalassaemi* or sickle or hemoglobinopath* or haemoglobinopath*) and (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*)):ti
#35 #33 or #34

PubMed (for Epub Ahead of Print, In-Process & Other Non-Indexed Citations only)

#1 ((adher* OR nonadher* OR complian* OR comply* OR noncomplian* OR noncomply* OR complier* OR noncomplier* OR accept* OR nonaccept* OR abandon* OR co-operat* OR cooperat* OR unco-operative* OR uncooperative* OR nonco-operat* OR noncooperat* OR satisfaction OR dissatisfaction OR persist* OR educat* OR questionnaire*) AND (patient OR patients OR treatment* OR therapy OR therapies OR medication* OR drug*))
#2 (patient dropout* OR patient drop* outs OR patients drop* out OR treatment* refus* OR refus* treatment*)
#3 #1 OR #2
#4 (deferoxamine* OR deferoximine* OR deferrioxamine* OR desferioximine* OR desferrioxamine* OR desferroxamine* OR desferal* OR desferral* OR DFO OR desferin* OR desferol* OR dfom OR deferiprone OR L1 OR kelfer OR DMHP OR ferriprox OR CP20 OR dmohpo OR hdmpp CPD OR hdpp OR exjade* OR deferasirox* OR ICL 670* OR icl670* OR CGP "72670" OR iron chelat* OR iron reduc* OR chelat* treatment* OR chelat* therapy)
#5 (thalassemi* OR thalassaemi* OR lepore OR hydrops fetalis OR cooley* anemi* OR cooley* anaemi*)
#6 (hemoglobin disease OR haemoglobin disease OR hemochromatosis OR haemochromatosis OR hemosiderosis OR haemosiderosis)
#7 (mediterranean anemi* OR mediterranean anaemi* OR erythroblastic anemi* OR erythroblastic anaemi*)
#8 hemoglobinopath* OR haemoglobinopath* OR iron overload* OR iron over-load*

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#9 ("sickle cell" OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
#10 #5 OR #6 OR #7 OR #8 OR #9
#11 #3 AND 4 AND #10
#12 ((adher*[TI] OR nonadher*[TI] OR complian*[TI] OR comply*[TI] OR noncomplian*[TI] OR noncomply*[TI] OR complier*[TI] OR noncomplier*[TI] OR accept*[TI] OR nonaccept*[TI] OR abandon*[TI] OR co-operat*[TI] OR cooperat*[TI] OR unco-operative*[TI] OR uncooperative*[TI] OR nonco-operat*[TI] OR noncooperat*[TI] OR satisfaction[TI] OR dissatisfaction[TI] OR persist*[TI] OR educat*[TI] OR questionnaire*[TI]) AND (thalassemia*[TI] OR thalassaemia*[TI] OR sickle[TI] OR iron overload*[TI]))
#13 #11 OR #12
#14 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#15 #13 AND #14

MEDLINE (OvidSP)

1. exp "Patient Acceptance of Health Care"/
2. (px or ed).fs.
3. "Patient Education as Topic"/
4. exp Data Collection/
5. (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*).ti.
6. ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) adj6 (patient* or treatment* or therapy or therapies or medication* or drug*)).ab,kf.
7. (patient* adj3 (dropout* or drop* out*)).tw,kf.
8. Treatment Refusal/
9. (treatment* adj3 refus*).tw,kf.
10. or/1-9
11. exp IRON CHELATING AGENTS/
12. CHELATION THERAPY/
13. (chelation adj3 (treatment* or therap*)).tw,kf.
14. (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom).mp.
15. (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp).mp.
16. (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670").mp.
17. (iron adj5 (chelat* or reduc*)).tw,kf.
18. or/11-17
19. exp THALASSEMIA/
20. (thalass?emi* or lepore or hydrops fetalis).tw,kf.
21. ((hemoglobin or haemoglobin) adj3 disease).tw,kf.
22. (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis).tw,kf.
23. ((mediterranean or erythroblastic or cooley*) adj (anemi* or anaemi*)).tw,kf.
24. exp IRON OVERLOAD/
25. (iron adj3 (overload* or over-load*)).tw,kf.
26. exp HEMOGLOBINOPATHIES/
27. exp HEMOGLOBIN, SICKLE/
28. (hemoglobinopath* or haemoglobinopath*).tw,kf.
29. exp ANEMIA, SICKLE CELL/
30. (barts and (blood or plasma)).tw,kf.
31. (sickle or sicklemi* or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf.

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32. (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*).tw,kf.
33. or/19-32
34. 10 and 18 and 33
35. exp *Hemoglobinopathies/ or (thalass?emi* or sickle or hemoglobinopath* or haemoglobinopath*).ti.
36. exp *Patient Compliance/ or (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*).ti.
37. 35 and 36
38. 34 or 37

Embase (OvidSP)

1. exp THALASSEMIA/
2. (thalass?emi* or lepore or hydrops fetalis).tw,kf.
3. ((hemoglobin or haemoglobin) adj3 disease).tw,kf.
4. (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis).tw,kf.
5. ((mediterranean or erythroblastic or cooley*) adj (anemi* or anaemi*)).tw,kf.
6. IRON OVERLOAD/
7. (iron adj3 (overload* or over-load*)).tw,kf.
8. HEMOGLOBINOPATHY/
9. HEMOGLOBIN S/
10. (hemoglobinopath* or haemoglobinopath*).tw,kf.
11. exp SICKLE CELL ANEMIA/
12. (barts and (blood or plasma)).tw,kf.
13. (sickle or sicklemi* or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf.
14. (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*).tw,kf.
15. or/1-14
16. exp PATIENT ATTITUDE/
17. PATIENT EDUCATION/
18. "PATIENT EDUCATION AS TOPIC"/
19. exp DATA COLLECTION METHOD/
20. (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*).ti.
21. ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) adj6 (patient* or treatment* or therapy or therapies or medication* or drug*)).ab,kf.
22. (patient* adj3 (dropout* or drop* out*)).tw.
23. (treatment* adj3 refus*).tw.
24. or/16-23
25. IRON CHELATING AGENT/
26. CHELATION THERAPY/
27. (chelation adj3 (treatment* or therap*)).tw,kf.
28. (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom).mp.
29. (deferiprone or L1* or kelfer or DMHP or ferriprox or cp20 or dmohpo or hdmpp CPD or hdpp).mp.
30. (exjade* or deferasirox* or (icl adj 670*) or icl670* or (cgp adj "72670")).mp.
31. (iron adj5 (chelat* or reduc*)).tw.
32. or/25-31
33. 15 and 24 and 32
34. exp *Hemoglobinopathy/ or (thalass?emi* or sickle or hemoglobinopath* or haemoglobinopath*).ti.

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35. exp *Patient Compliance/ or (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*).ti.
36. 34 and 35
37. 33 or 36

CINAHL (EBSCOHost)

S1 (MH "Patient Compliance+")
S2 (MH "Patient Education")
S3 (MH "Instrument by Type+")
S4 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*)
S5 AB ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) N6 (patient* or treatment* or therapy or therapies or medication* or drug*))
S6 TX (patient* N3 (dropout* or drop* out*))
S7 MH Treatment Refusal
S8 TX (treatment* N3 refus*)
9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Chelating Agents+")
S11 (MH "Chelation Therapy")
S12 TX (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom)
S13 TX (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp)
S14 TX (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670")
S15 TX (iron N5 (chelat* or reduc*)) OR TX (chelat* N3 (treatment* or therap*))
S16 S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17 (MH "Thalassemia+")
S18 TX (thalassemi* or thalassaemi* or lepore or hydrops fetalis)
S19 TX ((hemoglobin or haemoglobin) N3 disease)
S20 TX (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis)
S21 TX ((mediterranean or erythroblastic or cooley*) N1 (anemi* or anaemi*))
S22 (MH "Iron Overload+")
S23 TX (iron N3 (overload* or over-load*))
S24 (MH "Hemoglobinopathies")
S25 TX (hemoglobinopath* or haemoglobinopath*)
S26 (MH "Anemia, Sickle Cell+")
S27 TX (barts and (blood or plasma))
S28 TX (sickle OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
S29 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S30 S9 AND S16 AND S29
S31 (MM "Patient Compliance+")
S32 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*)
S33 S31 OR S32
S34 (MM "Hemoglobinopathies+")
S35 TI (thalassemi* or thalassaemi* or sickle or hemoglobinopath* or haemoglobinopath*)
S36 S34 OR S35

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S37 S33 AND S36
S38 S30 OR S37

PsycINFO (EBSCOHost) & EBSCOHost Psychology and Behavioral Sciences Collection

S1 DE "Treatment Compliance" OR DE "Compliance" OR DE "Treatment Refusal" OR DE "Treatment Dropouts" OR DE "Treatment Termination"
S2 DE "Client Education"
S3 DE "Questionnaires" OR DE "General Health Questionnaire"
S4 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*)
S5 AB ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) N6 (patient* or treatment* or therapy or therapies or medication* or drug*))
S6 TX (patient* N3 (dropout* or drop* out*))
S7 DE Treatment Refusal
S8 TX (treatment* N3 refus*)
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 TX (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom)
S11 TX (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp)
S12 TX (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670")
S13 TX (iron N5 (chelat* or reduc*)) OR TX (chelat* N3 (treatment* or therap*))
S14 S10 OR S11 OR S12 OR S13
S15 TX (thalassemi* or thalassaemi* or lepore or hydrops fetalis)
S16 TX ((hemoglobin or haemoglobin) N3 disease)
S17 TX (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis)
S18 TX ((mediterranean or erythroblastic or cooley*) N1 (anemi* or anaemi*))
S19 TX (iron N3 (overload* or over-load*))
S20 TX (hemoglobinopath* or haemoglobinopath*)
S21 DE "Sickle Cell Disease"
S22 TX (barts and (blood or plasma))
S23 TX (sickle OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
S24 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S25 S9 AND S14 AND S24
S26 MM "Treatment Compliance"
S27 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*)
S28 S26 OR S27
S29 MM "Sickle Cell Disease"
S30 TI (thalassemi* or thalassaemi* or sickle or hemoglobinopath* or haemoglobinopath*)
31 S29 OR S30
S32 S28 AND S31
S33 S25 OR S32

WEB OF SCIENCE CPCI-S

#1 TS=((adher* OR nonadher* OR complian* OR comply* OR noncomplian* OR noncomply* OR complier* OR noncomplier* OR accept* OR nonaccept* OR abandon* OR co-operat* OR cooperat* OR unco-operative* OR uncooperative* OR nonco-operat* OR noncooperat* OR satisfaction OR dissatisfaction OR persist* OR educat* OR questionnaire*) AND (patient* OR treatment* OR therapy OR therapies OR medication* OR drug*))

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#2 TS=(patient dropout* OR patient drop* outs OR patients drop* out OR treatment* refus* OR refus* treatment*)
#3 #1 OR #2
#4 TS=(deferoxamine* OR deferoximine* OR deferrioxamine* OR desferioximine* OR desferrioxamine* OR desferroxamine* OR desferal* OR desferral* OR DFO OR desferin* OR desferol* OR dfom OR deferiprone OR L1 OR kelfer OR DMHP OR ferriprox OR CP20 OR dmohpo OR hdmpp CPD OR hdpp OR exjade* OR deferasirox* OR ICL 670* OR icl670* OR CGP "72670" OR iron chelat* OR iron reduc* OR chelat* treatment* OR chelat* therap*)
#5 TS=(thalassemi* OR thalassaemi* OR lepore OR hydrops fetalis OR cooley* anemi* OR cooley* anaemi* OR hemoglobin disease OR haemoglobin disease OR hemochromatosis OR haemochromatosis OR hemosiderosis OR haemosiderosis OR mediterranean anemi* OR mediterranean anaemi* OR erythroblastic anemi* OR erythroblastic anaemi* OR iron overload* OR iron over-load* OR hemoglobinopath* OR haemoglobinopath*)
#6 TS=(sickle OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
#7 #5 OR #6
#8 #3 AND #4 AND #7

ProQuest Dissertations & Theses Global
ti(adher* OR nonadher* OR complian* OR comply* OR noncomplian* OR noncomply* OR complier* OR noncomplier* OR accept* OR nonaccept* OR abandon* OR co-operat* OR cooperat* OR unco-operative* OR uncooperative* OR nonco-operat* OR noncooperat* OR satisfaction OR dissatisfaction OR refus* OR persist* OR educat* OR questionnaire*) AND ti(thalassemia OR thalassaemia OR sickle OR sickled OR sickling OR iron overload OR hemoglobinopath*) AND (chelation OR chelating OR deferiprone OR deferoxamine OR deferasirox OR DFO OR ferriprox OR exjade OR iron reduction)
ClinicalTrials.gov
Search Terms: (thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies) AND (iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction)
WHO ICTRP
Condition: thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies
Intervention: iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction
ISRCTN
Condition: thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies
Interventions: iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction

Appendix 2. The Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) assessment tool

ROBINS-I tool (Stage I)

Specify the review question

Participants	
Experimental intervention	
Control intervention	

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(*Continued*)

Outcomes	

List the confounding areas relevant to all or most studies

List the possible co-interventions that could be different between intervention groups and could have an impact on outcomes

The ROBINS-I tool (Stage II): For each study

Specify a target trial specific to the study.

Design	Individually randomised or cluster randomised or matched
Participants	
Experimental intervention	
Control intervention	

Is your aim for this study...?

- ☐ to assess the effect of initiating intervention (as in an intention-to-treat analysis)
- ☐ to assess the effect of initiating and adhering to intervention (as in a per protocol analysis)

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed (or both).

Preliminary consideration of confounders

Complete a row for each important confounding area (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.
'Important' confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. 'Validity' refers to whether the confounding variable or variables fully measure the area, while 'reliability' refers to the precision of the measurement (more measurement error means less reliability).

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(i) Confounding areas listed in the review protocol				
Confounding area	Measured variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	OPTIONAL: is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / No / No information	Favour intervention / Favour control / No information

(ii) Additional confounding areas relevant to the setting of this particular study, or which the study authors identified as important				
Confounding area	Measured Variable(s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	OPTIONAL: is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / No / No information	Favour intervention / Favour control / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

'Important' co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

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(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

Risk of bias assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study? If **N** or **PN** to **1.1**: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equiv-	Y / PY / PN / N

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(*Continued*)

		alent to a fully randomised trial There is no NI (No information) option for this signalling question	
	If **Y** or **PY** to **1.1**: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? If **N** or**PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y** or**PY**, proceed to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If **N** or **PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y** or**PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required	NA / Y / PY / PN / N / NI
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding	NA / Y / PY / PN / N / NI
	1.5.**If Y** or **PY** to**1.4**: were confounding areas that were con-	Appropriate control of confounding requires that the vari-	NA / Y / PY / PN / N / NI

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	trolled for measured validly and reliably by the variables available in this study?	ables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings	
	1.6. Did the authors control for any post-intervention variables?	Controlling for post-intervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias	NA / Y / PY / PN / N / NI
	Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present	NA / Y / PY / PN / N / NI
	1.8. If**Y** or**PY** to**1.7**: Were confounding areas that were adjusted for measured validly and reliably by the variables avail-	See 1.5 above.	NA / Y / PY / PN / N / NI

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(*Continued*)

	able in this study?		
	Risk of bias judgement	**Low** - no confounding expected.	Low / Moderate / Serious / Critical / NI
		Moderate - confounding expected, all known important confounding domains appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	
		Serious - at least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding	
		Critical - confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding	
	Optional: what is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all im-	Favours experimental / Favours comparator / Unpredictable

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(*Continued*)

		portant confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact	
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding)	Y / PY / PN / N / NI
	If**N** or**PN** to**2.1**: go to 2.4		
	2.2. If**Y** or**PY** to**2.1**: were the post-intervention variables that influenced selection likely to be associated with intervention	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention and an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome	NA / Y / PY / PN / N / NI
	2.3 If **Y** or**PY** to**2.2:** were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
	2.4. Do start of follow up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention	Y / PY / PN / N / NI

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(*Continued*)

		will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses	
	2.5. If**Y** or**PY** to**2.2** and**2.3**, or **N** or**PN to 2.4**: were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be "No"	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - all participants who would have been eligible for the target trial were included in the study and start of follow up and start of intervention coincide for all subjects	Low / Moderate / Serious / Critical / NI
		Moderate - selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time	

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(*Continued*)

		Serious - selection into the study was related to intervention and outcome; or Start of follow up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time	
		Critical - selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time	
	Optional: what is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'	Y / PY / PN / N / NI

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	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - intervention status is well defined and based solely on information collected at the time of intervention	Low / Moderate / Serious / Critical / NI
		Moderate - intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively	
		Serious - intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome	
		Critical - (unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases	

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(*Continued*)

	Optional: what is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to departures from intended interventions	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administering the intervention?	Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. We distinguish between analyses where: (1) intervention switches led to follow up time being assigned to the new intervention; and (2) intervention switches (including cessation of intervention) where follow up time remained allocated to the original intervention; (3) is addressed under time-varying confounding, and should not be considered further here Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow up. Was lack of adherence sufficient to impact the intervention effect estimate?	NA/ Y / PY / PN / N / NI
	4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been ad-	NA/ Y / PY / PN / N / NI

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(*Continued*)

		ministered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups	
	4.4. If**N** or**PN** to**4.1, 4.2** or**4.3**: were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - no bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued	Low / Moderate / Serious / Critical / NI
		Moderate - bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention	
		Serious - switches in treatment, co-interventions, or problems with implementation fidelity	

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(*Continued*)

		are apparent and are not adjusted for in the analyses	
		Critical - substantial deviations from the intended intervention are present and are not adjusted for in the analysis	
	Optional: what is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to missing data	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the intended study sample is clear, which it may not be in practice	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis	Y / PY / PN / N / NI
	5.4 If **Y** or**PY to 5.1, 5.2** or**5.3**: are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to	NA / Y / PY / PN / N / NI

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		answer the question being addressed	
	5.5**If Y** or **PY** to**5.1, 5.2** or**5.3**: were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias	Low / Moderate / Serious / Critical / NI
		Moderate - proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis	
		Serious - proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis	

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		Critical - (unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis	
	Optional: what is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome de-	Y / PY / PN / N / NI

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		tection methods and thresholds, same time point, same definition, and same measurements	
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - the methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status	Low / Moderate / Serious / Critical / NI
		Moderate - the methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by	

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		study participants; and Any error in measuring the outcome is only minimally related to intervention status	
		Serious - the methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status	
		Critical - the methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups	
	Optional: what is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from..		
	7.1. ... multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI

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	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cutpoints; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not prespecify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - there is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses	Low / Moderate / Serious / Critical / NI

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		and sub-cohorts	
		Moderate - the outcome measurements and analyses are consistent with an *a priori* plan; or are clearly defined and both internally and externally consistent; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results	
		Serious - outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results	
		Critical - there is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results	
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Overall bias	**Risk of bias judgement**	**Low** - the study is judged to be at low risk of bias for all domains	Low / Moderate / Serious / Critical / NI

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		Moderate - the study is judged to be at low or moderate risk of bias for all domains	
		Serious - the study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain	
		Critical - the study is judged to be at critical risk of bias in at least one domain	
		No information - there is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)	
	Optional: what is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: conceiving the review, protocol development, content expert.
- Patricia Fortin: protocol development.
- Karen Madgwick: protocol development, content expert.
- Sally Hopewell: protocol development and methodological expert.
- Marialena Trivella: protocol development and statistical expert.

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