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Daily iron supplementation for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents (Protocol)

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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 4
METHODS 4
ACKNOWLEDGEMENTS 9
REFERENCES 10
APPENDICES 13
CONTRIBUTIONS OF AUTHORS 20
DECLARATIONS OF INTEREST 20
SOURCES OF SUPPORT 20
NOTES 21

[Intervention Protocol]

Daily iron supplementation for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents

Julia L Finkelstein[1], Heather S Herman[1], Heather M Guetterman[1], Juan Pablo Peña-Rosas[2], Saurabh Mehta[1]

[1]Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA. [2]Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Geneva, Switzerland

Contact address: Saurabh Mehta, Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA. smehta@cornell.edu.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the efficacy and safety of daily oral iron supplementation for prevention or treatment of iron deficiency anaemia in children and adolescents from birth less than 19 years of age.

BACKGROUND

Description of the condition

Anaemia

Anaemia is a widespread public health problem, affecting people in low-, middle-, and high-income countries, with detrimental health and economic consequences. Globally, anaemia was estimated to affect 800 million children and women in 2011, with the highest prevalence among preschool-age children (6 to 59 months; 42.6%) and pregnant women (15 to 49 years; 38.2%) (WHO 2015a). Regional estimates indicate that the greatest proportion of anaemic individuals resides in Africa (i.e. approximately 62%) and South-East Asia (i.e. 53.8%). Anaemia is defined as low haemoglobin concentrations according to World Health Organization (WHO) thresholds for varying life stages, adjusted for smoking status and elevation (WHO 2011a), and is characterised by insufficient erythropoiesis and lower oxygen-carrying capacity for red blood cells to meet physiological requirements (WHO 2011a).

Iron-deficiency anaemia

Iron deficiency is the leading cause of anaemia worldwide, accounting for approximately 50% of cases (95% confidence interval (CI) 47% to 53%) (WHO 2015a), with estimates ranging from 25% (Petry 2016), to over 60% (Kassebaum 2016). Iron deficiency is defined as inadequate mobilisable iron stores caused by long-term negative iron balance and depleted ferritin and haemosiderin stores (Auerbach 2016). Iron-deficiency anaemia is observed as the presence of both iron deficiency and anaemia and is accompanied by hypochromic microcytic red blood cells.

Causes of iron-deficiency anaemia vary by life stage. During the first few months of life, iron required for erythropoiesis is derived from foetal stores (Neuberger 2016), and from breast milk (Burke 2014). After stores are depleted by four to six months of age, de-

velopmental demands for iron increase beyond the amount available from breast milk (Black 2011), prompting the need for iron from complementary foods and supplementation. Infants born to anaemic or iron-deficient mothers, preterm infants, and those with low birth weight begin life with lower iron stores and are at higher risk for iron deficiency (Lönnerdal 2015; WHO 2017).

Rapid erythropoiesis, inadequate dietary consumption, limited bioavailability, and reduced absorption contribute to increased risk for iron deficiency throughout infancy and childhood (WHO 2016). School-age children consuming primarily unfortified cereal-based diets are at greater risk of iron deficiency owing to low iron content and bioavailability (WHO/FAO 2004). Non-haem iron, the form derived from plant sources, has lower bioavailability and is more sensitive to enhancers (e.g. ascorbic acid) and inhibitors (e.g. phytic acid, tannins) of iron absorption when compared to haem iron, the form derived from animal sources.

During adolescence, physiological demands increase to accommodate rapid growth and development. Adolescent girls and women (10 to 19 years) in particular are at increased risk of iron deficiency owing to menstrual blood loss and increased requirements during pregnancy for maternal metabolism and foetal growth (Camaschella 2017).

Other nutritional and non-nutritional types of anaemia

In addition to iron deficiency, other nutritional deficiencies, such as folate and vitamin B_{12} (Finkelstein 2015), contribute to the development of anaemia that manifests as megaloblastic anaemia (WHO 2017). Non-nutritional factors, such as infection and inflammation, also influence iron metabolism and can cause anaemia of inflammation, previously known as anaemia of chronic disease. In anaemia of inflammation, elevated inflammatory cytokines result in increased expression of hepcidin, a hepatic peptide hormone and regulator of iron homeostasis. Hepcidin limits iron availability to pathogens by decreasing systemic iron concentrations, resulting in iron sequestration and decreased iron delivery to tissues (Camaschella 2017). Consequently, anaemia of inflammation is characterised by adequate or high iron stores (i.e. serum ferritin) and low serum transferrin. In contrast to iron deficiency, anaemia of inflammation cannot be prevented or resolved by iron supplementation and may be exacerbated by iron interventions (Camaschella 2017).

Indicators of iron status

The variety and complexity of biomarkers for assessment of iron status pose challenges for evaluation of the efficacy of interventions for anaemia and iron-deficiency prevention and treatment. In addition to haemoglobin concentrations, WHO recommendations for iron status assessment of populations include serum ferritin and soluble transferrin receptor and at least one acute phase protein (e.g. C-reactive protein, alpha-1 acid glycoprotein) (WHO 2011b; WHO/CDC 2007). Worldwide, different organizations use different definitions of iron deficiency for the diagnosis and treatment of iron deficiency (Peyrin-Biroulet 2015). The World Health Organization is currently updating the ferritin thresholds to define iron deficiency in various population groups (Garcia-Casal 2014) to facilitate harmonization of the thresholds used in the presence of infection and inflammation (Suchdev 2017) and different laboratory methods (Garcia-Casal 2018).

Consequences of iron-deficiency anaemia

Iron is required for optimal growth and development (Lynch 2018; Stevens 2013). Iron deficiency can lead to impaired neural development and motor and cognitive function and increased risk of mortality (De-Regil 2011; Stevens 2013). Iron deficiency alters structural and metabolic components of the brain involved in memory and learning (i.e. hippocampus, basal ganglia, and cerebral cortex) by impairing oligodendrocyte functioning, myelin synthesis, brain energy utilisation, and neurotransmitter metabolism (Beard 2008; Estrada 2014). Neurotransmitters affected by iron (i.e. dopamine, epinephrine, and serotonin) are linked to sleep cycles, motor control, learning, and memory, and impairments may be irreversible (Lozoff 2006; Lozoff 2007). Iron deficiency and anaemia also impair activity of iron-dependent enzymes involved in cell proliferation, oxygen transport, and energy production (Camaschella 2017). This is particularly detrimental for periods of rapid growth during childhood.

Iron deficiency during childhood has also been associated with impaired immune function and increased severity of infection (Beard 2001; WHO 2001). The immune system requires iron for several enzymes and for cell production and differentiation and cytokine production. Previous studies in humans have noted an association between iron deficiency and decreased bactericidal activity of macrophages and activity and concentrations of several cytokines (Beard 2001).

Iron deficiency and iron-deficiency anaemia have also been associated with fatigue and diminished work productivity later in life (Horton 2006; Stevens 2013). This association has largely been attributed to the role of iron in oxidative energy production and oxygen transport through haemoglobin. Iron-deficiency anaemia has been associated with decreased aerobic capacity, endurance capacity, and economic productivity (Haas 2001).

Description of the intervention

This review will focus on daily administration of oral iron supplements (i.e. as tablet, capsule, dispersible tablet, syrup, or drops) and will include any form of iron compound, such as ferrous sulphate, ferrous gluconate, ferric pyrophosphate, and ferric citrate.

Potential adverse effects of the intervention

Iron supplementation has been associated with adverse effects, including mild gastrointestinal symptoms (Camaschella 2015). Administration of iron supplementation with meals may be associated with reduced occurrence of gastrointestinal side effects, but foods consumed concurrently may also influence iron absorption and metabolism (Lopez 2016). Adverse effects may be associated with reduced adherence to iron supplementation and may limit the effectiveness of interventions.

Malaria is concentrated in the same world areas as anaemia and affects the same risk population and the relationship between iron deficiency and malaria infection is complex (WHO 2018). Previous studies highlighted potential concerns regarding iron supplementation in malaria-endemic settings, including increased risks of malaria infection and mortality (Sazawal 2006). However, more recent evidence indicates that iron supplementation does not increase the risk of malaria in the context of effective malaria-control programmes, through which regular malaria prevention and treatment services are available (Neuberger 2016; WHO 2016). Currently, the WHO does not recommend screening for anaemia or iron deficiency before universal iron supplementation in malaria-endemic settings (WHO 2016). However, limited evidence is available for the occurrence of other adverse effects of iron supplementation, particularly in adolescents and young children.

How the intervention might work

The goal of iron supplementation interventions is to improve iron status by increasing haemoglobin concentrations and iron stores (Auerbach 2016). Iron supplementation may be used as an intervention both to prevent and to treat iron deficiency anaemia and iron deficiency in at-risk populations (Lopez 2016).

The nutritional composition of iron supplements and the timing of intake of supplements with meals may impact their efficacy owing to dietary enhancers (e.g. ascorbic acid) and inhibitors (e.g. phytic acid, tannins in coffee or tea) of iron absorption. Iron supplementation coupled with other micronutrients may also enhance iron absorption (e.g. vitamin C) and efficacy (e.g. folic acid, vitamin B_{12}) of iron for health outcomes.

Current recommendations

The World Health Organization currently recommends three consecutive months of supplemental provision of 10 mg to 12.5 mg of elemental iron daily for three months for prevention of anaemia and iron deficiency in children age 6 to 23 months who were born at term (WHO 2016). The recommended dose is increases to 30 mg of elemental iron daily for children age 24 to 59 months, and 30 mg to 60 mg daily for children 5 to 12 years of age and for menstruating, non-pregnant female adolescents, particularly in settings where the prevalence of anaemia is 40% or higher (WHO 2016). If a child receives the diagnosis of anaemia, the WHO recommends that clinicians should refer to national guidelines for treatment of anaemia (WHO 2016).

Why it is important to do this review

Anaemia affects an estimated 800 million children and women worldwide (WHO 2015a); the greatest burden is seen among young children, with 41.7% of children younger than 5 years affected in 2016 (World Bank 2018). It is estimated that approximately 50% of these cases are due to iron deficiency (95% CI 47% to 53%) (WHO 2015a).

The action plan of the 65th World Health Assembly for maternal, infant, and child nutrition included a commitment to reduce the prevalence of anaemia among women of reproductive age by 50% by 2025, but the plan did not provide a specific target for reducing the prevalence of anaemia or iron deficiency among children, who remain one of the most largely affected age groups (WHO 2015a). Objectives for 2030 of the Global Strategy for Women's, Children's, and Adolescents' Health include reducing under 5 (years) mortality to 25 per 1000 children, ending preventable deaths and malnutrition, and improving the likelihood of quality childhood development, all of which are related directly or indirectly to reduction of anaemia in children (WHO 2015b).

Randomised clinical trials to date have demonstrated the beneficial effects of iron supplementation on haematological parameters in children. Evidence to date suggests that iron supplementation improves iron status and cognitive and physical development and growth, and may reduce the occurrence of infectious disease morbidity in children (Thompson 2013), while reducing fatigue and improving work productivity later in life (Horton 2006; Stevens 2013). However, the 2016 WHO Guidelines on iron supplementation in infants and children emphasise gaps in evidence for longer-term functional outcomes, including anaemia, iron deficiency, iron deficiency anaemia, cognitive development, growth, and adverse effects (Low 2013; Pasricha 2013; Thompson 2013; WHO 2016).

Further, limited evidence is available on the efficacy of iron supplementation in adolescents - a population at high risk of anaemia and iron deficiency owing to increased requirements for rapid development and losses due to menstruation in female adolescents. It is important to determine if iron supplementation may treat and reverse iron deficiency early in life, and if ongoing supplementation prevents iron deficiency anaemia. Further research is needed to evaluate the efficacy of daily iron supplementation for longer-term clinical outcomes, including growth and development throughout infancy, childhood, and adolescence.

This review will complement other Cochrane systematic reviews on the effects of iron supplementation on iron status and health outcomes in at-risk populations. The effects of intermittent iron supplementation for children younger than 12 years, as examined in De-Regil 2011, and the effects of iron therapy (i.e. oral, intra-

muscular, or intravenous) on cognitive function and psychomotor development in children younger than 3 years of age, as discussed in Wang 2013, have been reviewed elsewhere. Other related Cochrane systematic reviews include those on effects of iron supplementation during pregnancy (Pena-Rosas 2015), efficacy and safety of iron supplementation for children in malaria-endemic regions (Neuberger 2016), and effects of iron supplementation in children with HIV infection (Adetifa 2009; Irlam 2013).

OBJECTIVES

To determine the efficacy and safety of daily oral iron supplementation for prevention or treatment of iron deficiency anaemia in children and adolescents from birth less than 19 years of age.

METHODS

Criteria for considering studies for this review

Types of studies

We will include the following trial designs.

- Randomised controlled trials (RCTs), with randomisation at the individual or cluster level.
- Quasi-RCTs (in which treatment has been allocated, for example, by alternate allocation, date of birth, alphabetical order, or another method).

Types of participants

Participants will include infants, children, and adolescents from birth to less than 19 years of age, regardless of baseline iron or anaemia status.

Diagnostic criteria for iron deficiency anaemia

Clinical presentation of iron deficiency anaemia in children includes pallor, fatigue, irritability, anorexia, delayed motor development, tachycardia, and splenomegaly (Lopez 2016). However, not all of these signs and symptoms are always present or specific to iron deficiency anaemia. Diagnosis of iron deficiency and iron deficiency anaemia requires confirmation through laboratory tests. Anaemia is diagnosed via low haemoglobin concentrations based on sex- and age-specific cutoffs. Laboratory tests for iron deficiency include measurements of ferritin, transferrin saturation, soluble transferrin receptor, and zinc-erythrocyte protoporphyrin. According to the WHO, iron status assessment should include haemoglobin, serum ferritin, and serum transferrin receptor concentrations, and at least one acute phase protein (e.g. C-reactive protein, α-1 acid glycoprotein) (WHO 2011b; WHO/CDC 2007). We plan to conduct sensitivity analyses of diagnostic criteria for iron deficiency and iron deficiency anaemia.

Types of interventions

This review will focus on daily administration of oral iron supplements and will consider any type or dose of iron compound compared to the same supplements without iron or to no treatment or placebo.

Daily oral iron supplementation includes delivery of iron compounds directly as a tablet, a capsule, or syrup given no less frequently than five days a week. Tablets (i.e. soluble tablets, effervescent tablets, oral tablets, and modified-release tablets) are solid dosage forms containing one or more active ingredients. Capsules are solid dosage forms with hard or soft shells that contain a single dose of one or more active ingredients. A dispersible tablet disintegrates in water or other liquids.

We have planned the following comparisons.

- Daily oral supplementation containing iron versus the same supplementation without iron.
- Daily oral supplementation with iron alone versus no treatment or placebo.
- Daily oral supplementation with iron + folic acid versus no treatment or placebo.
- Daily oral supplementation with iron + folic acid versus folic acid.
- Daily oral supplementation with iron + vitamins and minerals versus no treatment or placebo.
- Daily oral supplementation with iron + vitamins and minerals versus the same vitamins and minerals without iron supplementation.

Concomitant interventions will have to be the same in both intervention and comparator groups to establish fair comparisons. If a trial includes multiple arms, we will include any arm that meets the review inclusion criteria.

Minimum duration of intervention and follow-up

We will investigate interventions with duration of at least one week, with no minimum follow-up period.

We will define any follow-up period going beyond the original time frame for the primary outcome measure as specified in the power calculation of the trial's protocol as an extended follow-up period (also called 'open-label extension study') (Buch 2011; Megan 2012).

Summary of specific exclusion criteria

- Trials that assessed the effects of supplementation with multiple micronutrients containing iron or iron plus folic acid compared to supplementation with iron, iron plus folic acid, placebo, no treatment, or supplementation with varying doses or nutrients other than iron.
- Trials addressing the effects of intermittent (e.g. weekly, twice weekly) iron supplementation regimens in comparison to daily supplementation regimens.
- Trials of supplemental iron administered intramuscularly or intravenously, or conventional food fortification, biofortified crops, micronutrient powders, or whole foods.
- Pregnant women as participants (Pena-Rosas 2015), or participants with co-morbidities affecting iron absorption or metabolism (Adetifa 2009; Neuberger 2016).
- Lactating women as participants.
- Participants born with low birth weight (i.e. < 2500 g) or participants who were preterm (i.e. < 37 weeks' gestation) infants.
- Participants with HIV infection (Irlam 2013).
- Patients with co-morbidities affecting iron absorption or metabolism, including malaria.
- Individuals 19 years of age and older. If a trial includes more than 50% of participants within age range, we will include the trial.

Types of outcome measures

We will not exclude trials based on primary or secondary outcome measures reported. If none of our primary or secondary outcomes was reported, we will not include the trial but will provide some basic information in an additional table.

Primary outcomes

- Growth
- Morbidity
- Any adverse events

Secondary outcomes

- Anaemia
- Haemoglobin (g/L)
- Iron status
- Iron deficiency
- Iron-deficiency anaemia
- Cognitive function and motor skill development
- Health-related quality of life
- Socioeconomic effects
- All-cause mortality

Method of outcome measurements

- Growth: measured by height-for-age Z-score, weight-for-height Z-score, and weight-for-age Z-score in children > 2 years of age; length-for-age Z-score, weight-for-length Z-score, and weight-for-age Z-score in children ≤ 2 years of age
- Morbidity: defined by trial authors and measured as the proportion of children with at least one reported illness
- Adverse events: defined as the incidence of adverse events such as iron overload, clinical malaria, gastrointestinal symptoms (e.g. abdominal pain, vomiting, nausea, diarrhoea, constipation), and other infections or adverse effects as defined by trial authors
- Anaemia: haemoglobin concentrations below a cutoff defined by trial authors, with account age, altitude, and smoking considered when applicable
- Haemoglobin concentrations (g/L)
- Iron status: as measured by trial authors using indicators of iron status, such as ferritin, soluble transferrin receptor, transferrin, or iron-binding capacity
- Iron deficiency: defined by trial authors using indicators of iron status such as ferritin, transferrin, or iron-binding capacity
- Iron deficiency anaemia: defined by the presence of anaemia plus iron deficiency, as defined by trial authors
- Cognitive function and motor skill development: as assessed by trial authors. For example, school grades, test performance, intelligence testing, using validated instruments such as Bayley Mental Development Index (MDI), Bayley Psychomotor Development Index (PDI), Stanford-Binet Test, and DENVER II Developmental Screening Test
- Health-related quality of life: as defined by trial authors and evaluated by a validated instrument (e.g. 36-Item Short Form Health Survey (SF-36), EuroQol-5 dimensions (EQ-5D)) (EuroQol Group 1990; Ware 1992)
- Socioeconomic effects: as defined by trial authors; such as direct costs defined as admission or readmission rates, average length of stay, visits to general practitioner, accident/emergency visits, medication consumption, indirect costs defined as resources lost owing to illness of participant or family member
- All-cause mortality: defined as death from any cause

Timing of outcome measurements

- Adverse events, all-cause mortality, morbidity: measured at any time during the study period after participants were randomised to intervention or comparator groups
- Growth, anaemia, haemoglobin, iron status, iron deficiency, iron deficiency anaemia, cognitive function and motor skill development, health-related quality of life, socioeconomic effects: group outcomes will be measured over the short (immediately after intervention), medium (one to six months), and long (more than six months) term

Specification of key prognostic variables

- Age
- Baseline iron status
- Baseline haemoglobin concentrations

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database until recent and will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R); from 1946 onwards)
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature)
- Web of Science Core Collection
- BIOSIS
- POPLINE
- Bibliomap & TRoPHI
- OpenGrey
- IBECS
- PAHO
- WHO IRIS
- WPRO, IMSEAR, AFRO
- SCIELO
- WHOLIS
- LILACS (Latin American and Caribbean Health Science Information database)
- IndMED
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch/)
- ClinicalTrials.gov (www.clinicaltrials.gov)

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, systematic reviews, meta-analyses, and health technology assessment reports. In addition, we will contact the authors of included trials to obtain additional information on these studies and to identify any additional trials that are unpublished or ongoing.

We will not use abstracts or conference proceedings for data extraction because this information source does not fulfil the Consolidated Standards of Reporting Trials (CONSORT) requirements, which is "an evidence-based, minimum set of recommendations for reporting randomised trials" (CONSORT; Scherer 2007). We will present information on abstracts or conference proceedings in the 'Characteristics of studies awaiting classification' table.

Data collection and analysis

Selection of studies

Two review authors (HH, HG) will independently scan the abstract, title, or both, of every record we retrieve in the literature searches, to determine which trials we should assess further. We will obtain the full text of all potentially relevant records. We will resolve disagreements through consensus or by recourse to a third review author (SM, JLF). If we cannot resolve a disagreement, we will categorise the trial as a 'Study awaiting classification' and will contact the trial authors for clarification. We will present an adapted PRISMA flow diagram to show the process of trial selection (Liberati 2009).

Data extraction and management

For trials that fulfil our inclusion criteria, two review authors (HH, HG) will independently extract key participant and intervention characteristics. We will report data on efficacy outcomes and adverse events using standardised data extraction sheets from the CMED Group. We will resolve disagreements by discussion or, if required, by consultation with a third review author (SM, JLF).

We will provide information including trial identifier for potentially relevant ongoing trials, in the 'Characteristics of ongoing trials' table and in a joint appendix 'Matrix of trial endpoint (publications and trial documents)'. We will attempt to locate the protocol for each included trial and will report in a joint appendix primary, secondary, and other outcomes compared to data in publications. We will email all authors of included trials to enquire whether they would be willing to answer questions regarding their trials. We will present the results of this survey in an appendix. We will thereafter seek relevant missing information on the trial from the primary trial author(s), if required.

Duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we will maximise the information yield by collating all available data and will use the most complete data set aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary trial, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included trial. Furthermore, we will list duplicate publications, companion documents, multiple reports of a trial, and trial documents of excluded trials (such as trial registry

information) as secondary references under the study ID of the excluded trial.

Data from clinical trial registers

If data from included trials are available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we will make full use of this information and will extract the data. If there is also a full publication of the trial, we will collate and critically appraise all available data. If an included trial is marked as a completed study in a trials register but no additional information (study results, publication, or both) is available, we will add this trial to the 'Characteristics of studies awaiting classification' table.

Assessment of risk of bias in included studies

Two review authors (HH, HG) will independently assess the 'Risk of bias' of each included trial. We will resolve disagreements by consensus or by consultation with a third review author (SM, JLF). In case of disagreement, we will consult the rest of the group and will make a judgement based on consensus. If adequate information is not available from trial authors, trial protocols, or both, we will contact trial authors for missing data on 'Risk of bias' items. We will use the Cochrane 'Risk of bias' assessment tool (Higgins 2017), assigning assessments of low, high, or unclear risk of bias (for details, see Appendix 1; Appendix 2). We will evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* according to the criteria and associated categorisations contained therein (Higgins 2017).

Summary assessment of risk of bias

We will present a 'Risk of bias' graph and a 'Risk of bias' summary figure.
We will distinguish between self-reported and investigator-assessed and adjudicated outcome measures.
We will consider the following self-reported outcomes.

- Morbidity
- Adverse events
- Health-related quality of life
- Socioeconomic effects

We will consider the following outcomes to be investigator-assessed.

- Growth
- Morbidity
- Adverse events
- Anaemia
- Haemoglobin
- Iron status
- Iron deficiency
- Iron deficiency anaemia
- Cognitive and motor skill development
- Socioeconomic effects
- All-cause mortality

Risk of bias for a trial across outcomes

Some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In case of high risk of selection bias, we will mark all endpoints investigated in the associated trial as being at high risk. Otherwise, we will not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We will assess the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We consider low risk of bias to denote low risk of bias for all key domains, unclear risk to denote unclear risk of bias for one or more key domains, and high risk to denote high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains

These are the main summary assessments that we will incorporate into our judgements about the quality of evidence in the 'Summary of findings' tables. We will define outcomes as having low risk of bias when most information comes from trials at low risk of bias, unclear risk when most information comes from trials at low or unclear risk of bias, and high risk when a sufficient proportion of information comes from trials at high risk of bias.

Measures of treatment effect

When at least two included trials are available for a comparison of a given outcome, we will try to express dichotomous data as a risk ratio (RR) or an odds ratio (OR) with 95% CIs. For continuous outcomes measured on the same scale (e.g. haemoglobin in g/L), we will estimate the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes measuring the same underlying concept (e.g. cognitive and motor skill development) but using different measurement scales, we will calculate the standardised mean difference (SMD). We will express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome. If more than one comparison from the same trial is eligible for inclusion in the same meta-analysis, we will combine groups to create a single pair-wise comparison, or we will appropriately reduce the sample size so

that the same participants do not contribute multiply (splitting the 'shared' group into two or more groups). Although the latter approach offers some solution for adjusting the precision of the comparison, it does not account for correlation arising from inclusion of the same set of participants in multiple comparisons (Higgins 2011b).

We will attempt to re-analyse cluster-RCTs that have not appropriately adjusted for potential clustering of participants within clusters in their analyses. Variance of the intervention effects will be inflated by a design effect (DEFF). Calculation of a DEFF involves estimation of an intra cluster correlation (ICC). We will obtain estimates of ICCs by contacting trial authors or by imputing ICC values using either estimates from other included trials that report ICCs or external estimates from empirical research (e.g. Bell 2013). We plan to examine the impact of clustering by performing sensitivity analyses.

Studies with more than two treatment groups

For trials with more than two intervention groups (multi-arm studies), we will include the directly relevant arms only. When we identify trials with various relevant arms, we will combine the groups into a single pair-wise comparison (Higgins 2011a), and we will include the disaggregated data in the corresponding subgroup category. When the control group is shared by two or more trial arms, we will divide the control group (events and total population) over the number of relevant subgroup categories to avoid double-counting the participants.

Dealing with missing data

If possible, we will obtain missing data from the authors of included trials. We will carefully evaluate important numerical data such as screened, randomly assigned participants, as well as intention-to-treat and as-treated and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and imputation methods (e.g. last observation carried forward).

For trials for which the standard deviation of the outcome is not available at follow-up or cannot be re-created, we will standardise by the average of the pooled baseline standard deviation from trials in which this information was reported.

When included trials do not report means and standard deviations (SDs) for outcomes, and we do not receive requested information from trial authors, we will impute these values by estimating the mean and the variance from the median, the range, and the size of the sample (Hozo 2005).

We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we will report per outcome which trials were included with imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report trial results as the pooled effect estimate in a meta-analysis.

We will identify heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we will also consider the I^2 statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we find heterogeneity, we will attempt to determine possible reasons for this by examining individual trial and subgroup characteristics.

Assessment of reporting biases

If we include 10 or more trials that investigate a particular outcome, we will use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials), and publication bias (Sterne 2011). Therefore, we will interpret results carefully.

Data synthesis

We plan to undertake (or display) a meta-analysis only if we judge participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful. Unless good evidence shows homogeneous effects across trials of different methodological quality, we will primarily summarise low risk of bias data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects and will present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval requires at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we will use the Peto odds ratio method, provided there is no substantial imbalance between intervention and comparator group sizes, and intervention effects are not exceptionally large. In addition, we will perform statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and we plan to conduct the following subgroup analyses including investigation of interactions (Altman 2003). We will not conduct subgroup analyses of outcomes with fewer than four trials.

- Trials in low- and middle-income countries compared to those in high-income countries.
- Dose of elemental iron:
  - Children 0 to 23 months: less than 10 mg; 10 mg to 12.5 mg; greater than 12.5 mg;
  - Children 24 to 59 months: less than 30 mg, 30 mg or greater; and
  - Children 5 to 19 years: less than 30 mg; 30 mg to 60 mg; greater than 60 mg.
- Age: children < 6 months; children 6 to 23 months; children 24 to 59 months; children 5 to 9 years; adolescents 10 to 14 years; adolescents 15 to 17 years.
- Sex: female; male; mixed or not reported.
- Type of supplementation: capsule; tablet; syrup; dispersible tablet.
- Duration of intervention: < 3 months; ≥ 3 months.
- Type of iron compound: ferrous sulphate; ferrous gluconate; ferrous fumarate; ferric pyrophosphate.

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting analysis to the following.

- Published trials.
- Effect of risk of bias, as specified in the Assessment of risk of bias in included studies section.
- With large sample size or extended follow-up, to establish the extent to which these factors influence the results.
- Use of the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry vs other), or country.

We will examine the robustness of results by repeating analyses using different measures of effect size (i.e. RR, OR, etc.) and different statistical models (i.e. fixed-effect and random-effects models).

Certainty of the evidence

We will present the overall certainty of evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. Two review authors (HH, HG) will independently rate the certainty of evidence for each outcome. We will resolve differences in assessment by discussion or by consultation with a third review author (SM, JLF).
We will include an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader 2014). Alternatively, we will use the GRADEpro Guideline Development Tool (GDT) software and will present evidence profile tables as an appendix (GRADEproGDT 2015). We will present results for outcomes as described in the Types of outcome measures section. If meta-analysis is not possible, we will present the results in a narrative format in the 'Summary of findings' table. We will justify all decisions to downgrade the quality of trials by using footnotes, and we will make comments to aid the reader's understanding of the Cochrane Review when necessary.

'Summary of findings' table

We will present a summary of the evidence in a 'Summary of findings' table. This will provide key information about the best estimate of the magnitude of effect in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We will create the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011), along with Review Manager (RevMan 5.3) table editor (RevMan 2014). We will report the following outcomes, listed according to priority.

- Growth
- Cognitive function and motor skill development
- Morbidity
- All-cause mortality
- Adverse events
- Iron deficiency anaemia
- Health-related quality of life.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. 'Risk of bias' assessment

'Risk of bias' domains
Random sequence generation (selection bias due to inadequate generation of a randomised sequence) For each included trial, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups • Low risk of bias: trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider use of the minimisation technique as equivalent to being random. • Unclear risk of bias: insufficient information about the sequence generation process. • High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

(*Continued*)

Allocation concealment (selection bias due to inadequate concealment of allocation before assignment)
We will describe for each included trial the method used to conceal allocation to interventions before assignment, and we will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgement for selection bias (Corbett 2014). Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between trials that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judge as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We will reclassify judgements of unclear, low, or high risk of selection bias as specified in Appendix 2.

Blinding of participants and study personnel (performance bias due to knowledge of allocated interventions by participants and personnel during the trial)
We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below)

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)
We will evaluate the risk of detection bias separately for each outcome (Hróbjartsson 2013). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below)

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to quantity, nature, or handling of incomplete outcome data)
For each included trial and/or each outcome, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the trial reported attrition and exclusions, and we will report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We will also note if the trial reported the reasons for attrition or exclusion, and whether missing data were balanced across groups or were related to outcomes. We will consider the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between trial arms)

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the trial did not address this outcome.

(*Continued*)

- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was enough to induce clinically relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them into a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

Other bias

- Low risk of bias: the trial appears to be free from other sources of bias.
- Unclear risk of bias: information was insufficient to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

Appendix 2. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone versus results obtained using method details and trial baseline information[a]

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from study characteristics data	Risk of bias using baseline information and methods reporting
Methods are unclear	Unclear risk	Baseline imbalances present for important prognostic variable(s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk

(*Continued*)

	Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	**Unclear risk**[b]
			Groups appear similar at baseline for all important prognostic variables	Low risk
			Limited baseline details, showing balance in some important prognostic variables[c]	Low risk
			No baseline details	**Unclear risk**
	Sequence is not truly randomised or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
			Groups appear similar at baseline for all important prognostic variables	**Low risk**
			Limited baseline details, showing balance in some important prognostic variables[c]	**Unclear risk**
			No baseline details	High risk

[a]Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias compared with using methods reporting alone.
[b]Imbalance was identified that appears likely to be due to chance.
[c]Details for the remaining important prognostic variables are not reported

Appendix 3. Search strategies

MEDLINE (OvidSP)
1. exp Iron compounds/ or Iron/ or Anemia, Iron-Deficiency/
2. (Iron or ferr*).tw
3. 1 or 2
4. exp dietary supplements/
5. (supplement* or pill* or oral* or capsule* or tablet* or liquid*).tw
6. 4 or 5
7. 3 and 6
8. exp Infant/
9. exp Child/

(*Continued*)

10. Adolescent/
11. exp Pediatrics/
12. Minors/
13. infan*.tw.
14. perinat*.tw.
15. neonat*.tw.
16. (baby* or babies).tw.
17. toddler*.tw.
18. minors*.tw.
19. (boy or boys or boyfriend or boyhood).tw.
20. girl*.tw.
21. (child* or children*).tw.
22. (kid* or kids*).tw
23. (schoolchild* or school*).tw.
24. adolescen*.tw.
25. juvenil*.tw.
26. youth*.tw.
27. (teen* or preteen*).tw.
28. (underage* or under age*).tw.
29. pubescen*.tw.
30. (pediatric* or paediatric* or peadiatric*).tw.
31. prematur*.tw.
32. preterm*.tw.
33. or/8-32
34. ("randomized controlled trial" or "controlled clinical trial").pt
35. (drug therapy).fs.
36. (randomized or placebo or randomly or trial or groups).ab
37. 34 or 35 or 36
38. 7 and 33 and 37
39. exp animals/ not humans/
40. 38 NOT 39

CENTRAL (Cochrane Library)

#1 MESH DESCRIPTOR Iron Compounds EXPLODE ALL TREES
#2 MESH DESCRIPTOR Iron
#3 MESH DESCRIPTOR Anemia, Iron-Deficiency
#4 #1 OR #2 OR #3
#5 (iron OR ferr*):TI,AB,KY
#6 #4 OR #5
#7 MESH DESCRIPTOR Dietary Supplements EXPLODE ALL TREES
#8 (supplement* OR pill* OR oral* OR capsule* OR tablet* OR liquid*):TI,AB
#9 #7 OR #8
#10 #6 AND #9
#11 MESH DESCRIPTOR Infant EXPLODE ALL TREES
#12 MESH DESCRIPTOR Child EXPLODE ALL TREES
#13 MESH DESCRIPTOR Adolescent
#14 MESH DESCRIPTOR Pediatrics EXPLODE ALL TREES
#15 MESH DESCRIPTOR Minors

(*Continued*)

#16 #11 OR #12 OR #13 OR #14 OR #15
#17 (infant* OR baby OR babies OR newborn* OR neonat* OR perinat* OR toddler* OR minors* OR child* OR preschool* OR schoolchild* OR school* OR boy* OR girl* OR kid OR kids OR teen* OR adolescen* OR preteen* OR juvenile* OR underage* OR under age* OR pubescen* OR pediatric* OR paediatric* PR peadiatric* OR prematur* OR preterm* OR youth* OR young person* OR young people OR young adult*):TI,AB,KY
#18 #16 OR #17
#19 #10 AND #18

CINAHL (EBSCO)

S1. MH ("iron compounds+" or Iron+ or Anemia+)
S2. TX (iron OR ferr*)
S3. S1 OR S2
S4. MH ("dietary supplements+")
S5. TX (supplement* OR pill* OR oral* OR capsule* OR tablet* OR liquid*)
S6. S4 OR S5
S7. S3 AND S5
S8. MH ("child+" OR "adolescence+" OR "pediatrics+")
S9. TX (infant* OR baby OR babies OR newborn* OR neonat* OR perinat* OR toddler* OR minors* OR child* OR preschool* OR schoolchild* OR school* OR boy* OR girl* OR kid OR kids OR teen* OR adolescen* OR preteen* OR juvenile* OR underage* OR "under age*" OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm* OR youth* OR "young person*" OR "young people" OR "young adult*")
S10. S8 OR S9
S11. MH "prognosis+" OR MH "study design+" or random*
S12. S7 AND S10 AND S11

Web of Science and BIOSIS

1. TS=(iron OR ferr*)
2. TS=(supplement* OR pill* OR oral* OR capsule* OR tablet* OR liquid*)
3. 1 AND 2
4. TS=(infant* OR baby OR babies OR newborn* OR neonat* OR perinat* OR toddler* OR minors* OR child* OR preschool* OR schoolchild* OR school* OR boy* OR girl* OR kid OR kids OR teen* OR adolescen* OR preteen* OR juvenile* OR underage* OR under age* OR pubescen* OR pediatric* OR paediatric* PR peadiatric* OR prematur* OR preterm* OR youth* OR young person* OR young people OR young adult*)
5. TS=("clinical trial*" OR "research design" OR "comparative stud*" OR "evaluation stud*" OR "controlled trial*" OR "follow-up stud*" OR "prospective stud*" OR random* OR placebo* OR "single blind*" OR "double blind*")
6. 3 AND 4 AND 5

POPLINE

((iron OR ferric OR ferrous) AND (supplement* OR pill* OR oral* OR capsule* OR tablet* OR liquid*))
AND
(infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR "school child*" OR boy* OR girl* OR pre-school* OR teen* OR adolescen* OR preteen* OR youth* OR "young person*" OR "young people" OR "young adult*")

Bibliomap & TRoPHI

(*Continued*)

Freetext: iron AND child* Freetext: iron AND infant* Freetext: iron AND neonat* Freetext: iron AND toddler* Freetext: iron AND bab* Freetext: iron AND newborn* Freetext: iron AND teen* Freetext: iron AND adolescen* Freetext: iron AND young
OpenGrey, IBECS, PAHO/WHO IRIS, WPRO, IMSEAR, AFRO, SCIELO
("iron supplement*" OR "iron pill*" OR "iron capsule*" OR "iron tablet*" OR "iron liquid*" OR "ferric supplement*" OR "ferric pill*" OR "ferric capsule*" OR "ferric tablet*" OR "ferric liquid*" OR "ferrous supplement*" OR "ferrous pill*" OR "ferrous capsule*" OR "ferrous tablet*" OR "ferrous liquid*") AND (infant* OR baby OR babies OR newborn* OR neonat* OR toddler* OR child* OR preschool* OR schoolchild* OR "school child*" OR boy* OR girl* OR pre-school* OR teen* OR adolescen* OR preteen* OR youth* OR "young person*" OR "young people" OR "young adult*")
WHOLIS
iron AND child* iron AND infant*
LILACS (iAHX interface)
(MH:"Iron compounds" OR MH:"Iron" OR MH:"Anemia, Iron-Deficiency" OR iron OR ferr$) AND (MH:"Dietary supplements" OR supplement$ OR pill$ OR oral$ OR capsule$ OR tablet$ OR liquid$) AND (MH:"Infant" OR MH:"Child" OR MH:"Adolescent" OR MH:"Pediatrics" OR MH:"Minors" OR infan$ OR baby OR babies OR newborn$ OR perinat$ OR neonat$ OR toddler$ OR minors$ OR child$ OR preschool$ OR schoolchild$ OR school$ OR boy OR boys OR boyhood OR underage$ OR under age$ OR pubescen$ OR pediatric$ or paediatric$ or peadiatric$ OR prematur$ OR preterm$ OR girl$ OR pre-school$ OR teen$ OR adolescen$ OR preteen$ OR youth$ OR) + *Filter "Controlled Clinical Trial" in right hand menu*
IndMED
(iron or ferr) and (supplement OR supplementation OR pill OR oral OR capsule OR tablet OR liquid) and (infants OR baby OR babies OR newborn OR neonates OR toddlers OR child OR children OR preschool OR schoolchildren OR boys OR girls OR pre-school OR teenagers OR adolescents OR preteens OR youth)
WHO ICTRP (Standard search)

(*Continued*)

iron* AND supplement* AND child* OR iron* AND supplement* AND infant* OR iron* AND supplement* AND bab* OR iron* AND supplement* AND newborn* OR iron* AND supplement* AND neonat* OR iron* AND supplement* AND toddler* OR iron* AND supplement* AND school* OR iron* AND supplement* AND boy* OR iron* AND supplement* AND girl* OR iron* AND supplement* AND teen* OR iron* AND supplement* AND kids OR iron* AND supplement* AND adolescen* OR iron* AND supplement* AND underage* OR iron* AND supplement* AND juvenil* OR iron* AND supplement* AND pubescen* OR iron* AND supplement* AND pediatric* OR iron* AND supplement* AND paediatric*
ClinicalTrials.gov (Advanced search)
Other terms: (iron OR ferric OR ferrous OR ferritin) AND (supplement OR supplements OR supplementation OR supplemented) Age Group: Child (birth-17)

CONTRIBUTIONS OF AUTHORS

All review authors developed this protocol and read and approved the final version.

DECLARATIONS OF INTEREST

Julia L Finkelstein (JLF): no conflicts of interest to declare.

Heather S Herman (HSH): no conflicts of interest to declare.

Heather M Guetterman (HG): no conflicts of interest to declare.

Saurabh Mehta (SM): has an equity interest in a start-up commercialising point-of-care diagnostic technology for nutritional status developed in his laboratory as a faculty member at Cornell University. SM is also a principal investigator on competitive grants to conduct trials with iron-biofortified crops as an intervention to improve health and related outcomes in children.

Juan Pablo Peña-Rosas (JPPR): no conflicts of interest to declare.

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Internal sources

- No sources of support supplied

External sources

- World Health Organization, Switzerland.

NOTES

We have based parts of the Methods, as well as Appendix 3, Appendix 1, and Appendix 2 of this Cochrane Protocol, on a standard template established by the CMED Group.