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

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

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

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## ABSTRACT

### Background

Regularly transfused people with sickle cell disease (SCD) and people with thalassaemia (who are transfusion-dependent or non-transfusion-dependent) are at risk of iron overload. Iron overload can lead to iron toxicity in vulnerable organs such as the heart, liver and endocrine glands; which can be prevented and treated with iron chelating agents. The intensive demands and uncomfortable side effects of therapy can have a negative impact on daily activities and well-being, which may affect adherence.

### Objectives

To identify and assess the effectiveness of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions) to improve adherence to iron chelation therapy in people with SCD or thalassaemia.

### Search methods

We searched CENTRAL (the Cochrane Library), MEDLINE, Embase, CINAHL, PsycINFO, Psychology and Behavioral Sciences Collection, Web of Science Science & Social Sciences Conference Proceedings Indexes and ongoing trial databases (01 February 2017). We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register (12 December 2017).

### Selection criteria

For trials comparing medications or medication changes, only randomised controlled trials (RCTs) were eligible for inclusion.

For studies including psychological and psychosocial interventions, educational Interventions, or multi-component interventions, non-RCTs, controlled before-after studies, and interrupted time series studies with adherence as a primary outcome were also eligible for inclusion.

### Data collection and analysis

Three authors independently assessed trial eligibility, risk of bias and extracted data. The quality of the evidence was assessed using GRADE.

## Main results

We included 16 RCTs (1525 participants) published between 1997 and 2017. Most participants had  $\beta$ -thalassaemia major; 195 had SCD and 88 had  $\beta$ -thalassaemia intermedia. Mean age ranged from 11 to 41 years. One trial was of medication management and 15 RCTs were of medication interventions. Medications assessed were subcutaneous deferoxamine, and two oral-chelating agents, deferiprone and deferasirox.

We rated the quality of evidence as low to very low across all outcomes identified in this review.

Three trials measured quality of life (QoL) with validated instruments, but provided no analysable data and reported no difference in QoL.

### Deferiprone versus deferoxamine

We are uncertain whether deferiprone increases adherence to iron chelation therapy (four trials, very low-quality evidence). Results could not be combined due to considerable heterogeneity (participants' age and different medication regimens). Medication adherence was high (deferiprone (85% to 94.9%); deferoxamine (71.6% to 93%)).

We are uncertain whether deferiprone increases the risk of agranulocytosis, risk ratio (RR) 7.88 (99% confidence interval (CI) 0.18 to 352.39); or has any effect on all-cause mortality, RR 0.44 (95% CI 0.12 to 1.63) (one trial; 88 participants; very low-quality evidence).

### Deferasirox versus deferoxamine

We are uncertain whether deferasirox increases adherence to iron chelation therapy, mean difference (MD) -1.40 (95% CI -3.66 to 0.86) (one trial; 197 participants; very-low quality evidence). Medication adherence was high (deferasirox (99%); deferoxamine (100%)). We are uncertain whether deferasirox decreases the risk of thalassaemia-related serious adverse events (SAEs), RR 0.95 (95% CI 0.41 to 2.17); or all-cause mortality, RR 0.96 (95% CI 0.06 to 15.06) (two trials; 240 participants; very low-quality evidence).

We are uncertain whether deferasirox decreases the risk of SCD-related pain crises, RR 1.05 (95% CI 0.68 to 1.62); or other SCD-related SAEs, RR 1.08 (95% CI 0.77 to 1.51) (one trial; 195 participants; very low-quality evidence).

### Deferasirox film-coated tablet (FCT) versus deferasirox dispersible tablet (DT)

Deferasirox FCT may make little or no difference to adherence, RR 1.10 (95% CI 0.99 to 1.22) (one trial; 173 participants; low-quality evidence). Medication adherence was high (FCT (92.9%); DT (85.3%)).

We are uncertain if deferasirox FCT increases the incidence of SAEs, RR 1.22 (95% CI 0.62 to 2.37); or all-cause mortality, RR 2.97 (95% CI 0.12 to 71.81) (one trial; 173 participants; very low-quality evidence).

### Deferiprone and deferoxamine combined versus deferiprone alone

We are uncertain if deferiprone and deferoxamine combined increases adherence to iron chelation therapy (very low-quality evidence). Medication adherence was high (deferiprone 92.7% (range 37% to 100%) to 93.6% (range 56% to 100%); deferoxamine 70.6% (range 25% to 100%).

Combination therapy may make little or no difference to the risk of SAEs, RR 0.15 (95% CI 0.01 to 2.81) (one trial; 213 participants; low-quality evidence).

We are uncertain if combination therapy decreases all-cause mortality, RR 0.77 (95% CI 0.18 to 3.35) (two trials; 237 participants; very low-quality evidence).

### Deferiprone and deferoxamine combined versus deferoxamine alone

Deferiprone and deferoxamine combined may have little or no effect on adherence to iron chelation therapy (four trials; 216 participants; low-quality evidence). Medication adherence was high (deferoxamine 91.4% to 96.1%; deferiprone: 82.4%)

Deferiprone and deferoxamine combined, may have little or no difference in SAEs or mortality (low-quality evidence). No SAEs occurred in three trials and were not reported in one trial. No deaths occurred in two trials and were not reported in two trials.

### Deferiprone and deferoxamine combined versus deferiprone and deferasirox combined

Deferiprone and deferasirox combined may improve adherence to iron chelation therapy, RR 0.84 (95% CI 0.72 to 0.99) (one trial; 96 participants; low-quality evidence). Medication adherence was high (deferiprone and deferoxamine: 80%; deferiprone and deferasirox: 95%).

We are uncertain if deferiprone and deferasirox decreases the incidence of SAEs, RR 1.00 (95% CI 0.06 to 15.53) (one trial; 96 participants; very low-quality evidence).

There were no deaths in the trial (low-quality evidence).

### ***Medication management versus standard care***

We are uncertain if medication management improves health-related QoL (one trial; 48 participants; very low-quality evidence). Adherence was only measured in one arm of the trial.

### **Authors' conclusions**

The medication comparisons included in this review had higher than average adherence rates not accounted for by differences in medication administration or side effects.

Participants may have been selected based on higher adherence to trial medications at baseline. Also, within the clinical trial context, there is increased attention and involvement of clinicians, thus high adherence rates may be an artefact of trial participation.

Real-world, pragmatic trials in community and clinic settings are needed that examine both confirmed or unconfirmed adherence strategies that may increase adherence to iron chelation therapy.

Due to lack of evidence this review cannot comment on intervention strategies for different age groups.

## **PLAIN LANGUAGE SUMMARY**

### **Strategies to increase adherence to iron chelation therapy in people with sickle cell disease or thalassaemia**

#### **Review question**

We wanted to determine if there are any interventions (medication, psychological or educational) that would help people adhere to their iron chelation therapy.

#### **Background**

People with sickle cell disease or thalassaemia who receive regular transfusions, are exposed to iron overload which can result in toxicity to organs and death. Iron chelation therapy is used to prevent or treat iron overload, but it can be a demanding regimen, and have unwanted side effects. There are three types of iron chelators being used to treat iron overload: deferoxamine given subcutaneously (by injecting a drug into the tissue layer between the skin and the muscle); and two agents that are taken orally, deferiprone and deferasirox.

#### **Search date**

The evidence is current to 12 December 2017.

#### **Study characteristics**

We searched the literature for both randomised and non-randomised studies, and found 16 randomised trials with 1525 participants, published between 1997 and 2017. Most people had  $\beta$ -thalassaemia major; one trial included people with SCD and one included people with a milder form of thalassaemia (thalassaemia intermedia). Mean age ranged from 11 years to 41 years. We included one trial of medication management and 15 trials comparing different drug treatments.

#### **Key results**

Trials included comparisons of individual agents to each other or a combination of drugs compared to one drug alone or to other combinations of drugs.

We were uncertain if single agents or combined agents made any difference in adherence rates, serious adverse events or mortality. Quality of life, measured using validated questionnaires, was only reported in two trials, but not enough data were reported to determine any differences between treatments.

There was no evidence on intervention strategies for different age groups.

We found that there was an unusually high adherence rate to all drugs and combinations of drugs in all the trials. This may be because participants may have been selected based on their ability to stick to medication regimens. Also, adherence may increase in trial participants when there is a higher level of clinician involvement in care.

We concluded that real-world randomised and non-randomised trials, run in both the community and in clinics, are needed to examine a variety of proven and unproven strategies that may be useful for increasing adherence to iron chelation therapy.

### **Quality of evidence**

We rated the quality of evidence as low to very low across all of the outcomes in this review. This was due to trials being at serious or very serious risk of bias; outcome estimates being imprecise (wide confidence intervals); and not widely applicable (with some trials conducted only in children of a specific age and meeting specific criteria).

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

DFP compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFP <b>Comparison:</b> DFO						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFO	Risk with DFP				
<b>Adherence to iron chelation therapy</b> (per cent, SD)			-	242 (4 RCTs)	⊕○○○ VERY LOW <sup>12</sup>	We found considerable heterogeneity and identified age as possible cause: 1 trial in children 10 years or older and 1 conducted in participants 18 or older
<b>SAEs (from therapy, disease, non-adherence)</b> Agranulocytosis**	Study population		RR 7.88 (99%CI 0.18 to 352.39)	88 (1 RCT)	⊕○○○ VERY LOW <sup>34</sup>	No SAEs were reported in the second trial reporting this outcome
	15 per 1000	118 per 1,000 (7 to 1000)				
<b>All-cause mortality</b>	Study population		RR 0.44 (95%CI 0.12 to 1.63)	88 (1 RCT)	⊕○○○ VERY LOW <sup>34</sup>	No deaths occurred in the second trial reporting this outcome
	146 per 1000	64 per 1000 (18 to 239)				
<b>Sustained adherence</b> - not measured	-	-	-	-	-	Sustained adherence is reported as adherence as all trials were longer than 6 months and only end of trial adherence

					numbers were provided
Quality of life - not reported	-	-	-	-	-

\***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; DFO: deferoxamine; DFP: deferiprone; RCT: randomised controlled trial; RR: risk ratio; SD: standard deviation.

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence by 1 for risk of bias due to high or uncertain risk of bias due to lack of blinding of participants and personnel in all four RCTs, as well as selection bias (Olivieri 1997), attrition bias (El Beshlawy 2008; Olivieri 1997), reporting bias (El Beshlawy 2008; Pennell 2006), and other bias (Pennell 2006).

<sup>2</sup> We downgraded the quality of evidence by 2 for inconsistency due to considerable heterogeneity in comparison.

<sup>3</sup> We downgraded the quality of evidence by 2 for imprecision due to very wide CIs that included clinically important benefits and harms.

<sup>4</sup> We downgraded the quality of evidence by 1 for indirectness as the trial was conducted in participants with thalassaemia intermedia only; a milder form of thalassaemia

\*\* Risk estimate based on: Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. *American Journal of Hematology*. 2016;91(10):1026-1031. doi:10.1002/ajh.24479.



## 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

SCD 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 (Pleasant 2014). It is one of the most common severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes (Rees 2010). Populations originating from sub-Saharan Africa, 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 mortality and increasing migration from highly affected countries have made this a worldwide problem (Piel 2012). Over 12,500 people in the UK and 100,000 in the USA suffer from the disease (NICE 2010; Pleasant 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 ( $\beta$ S) alleles (haemoglobin (Hb)SS). The second most common genotype (up to 30% of cases in people of African origin) is haemoglobin SC disease (HbSC disease) and is due to the co-inheritance of the  $\beta$ S and  $\beta$ C alleles; this tends to be a more moderate form of the disease. The third major type of SCD occurs when  $\beta$ S is inherited with a  $\beta$ -thalassaemia allele, causing HbS/ $\beta$ -thalassaemia (Rees 2010). People who have inherited a thalassaemia null mutation (HbS $\beta^0$ ) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbS $\beta^+$  thalassaemia have a milder disorder. In high-income nations, people with SCD are expected to live into their 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  $\alpha$  or  $\beta$  globin chain ( $\alpha$ -thalassaemia,  $\beta$ -thalassaemia or H disease). In  $\beta$ -thalassaemia, reduced or absent  $\beta$  globulin production leads to an excess of free  $\alpha$ -globin chains resulting in severe anaemia and bone marrow hyperplasia (abnormal cell growth) preventing normal development. In H disease and  $\alpha$ -thalassaemia, the  $\alpha$ -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 Mediterranean, 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,  $\beta$ -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  $\beta$ -thalassaemia major, or in people when DFO is contraindicated.

cated 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).

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, an 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 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 (QoL) 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 QoL (NCCMH 2010; NCCPC 2009). The use of cognitive aids, clear instructions and realistic expectations can improve adherence (Wertheimer 2003). Person-centred 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, lifestyle 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 minimise harms and improve outcomes, combined with medication reconciliation strategies including audit and feedback, prescription and medication help lines, counselling and age-appropriate discharge instructions, may help to address and improve adherence (NCCPC 2009; Ryan 2014). Medication interventions also include medication management which is a person-centred intervention by a clinician (often a pharmacist) to optimise drug therapy in order to improve outcomes for the person (American Pharmacists Association 2008).

## 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 (which include comparisons of adherence between different iron chelators), 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 included randomised controlled trials (RCTs) comparing one or more adherence interventions, to standard care.

For studies comparing medications or medication changes, we only included RCTs.

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

We planned to include cluster-randomised trials, non-randomised cluster trials, and CBA studies if they had at least two intervention sites and two control sites. We excluded cluster-randomised trials, non-randomised cluster trials, and CBA studies that had only one intervention or control site because the intervention (or comparison) may 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 planned to include ITS and repeated measures studies which had a clearly defined point in time when the intervention occurred and at least three data points before and after the intervention. We excluded ITS studies that did not have a clearly defined point in time when the intervention occurred, or fewer than three data points before and after the intervention, or the ITS study ignored secular (trend) changes, performed a simple t-test of the pre- versus post-intervention periods and re-analysis of the data was not possible (in accordance with [EPOC 2015](#) 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

- Standard care (as defined in the trial)

## 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 categorised all-cause mortality and SAEs according to short-, medium-, and long-term outcomes. We reported the exact definition of these time frames over time periods that are common to as many trials 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 QoL (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 categorised health-related QoL, iron overload and organ damage according to short-, medium-, and long-term outcomes. We reported 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

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

### Electronic searches

We identified 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 Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); 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's [website](#).

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 12 December 2017.

In addition to the above, we conducted a search of the following databases to include RCTs, NRSIs, CBA and ITS studies:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) and Other Reviews (DARE; 2015, Issue 2) ( [www.cochranelibrary.com/](http://www.cochranelibrary.com/)) searched 01 February 2017;
- PubMed (Epub Ahead of Print, In-Process and Other Non-Indexed Citations, for recent records not yet added to MEDLINE) ( [www.ncbi.nlm.nih.gov/sites/entrez](http://www.ncbi.nlm.nih.gov/sites/entrez)) searched 01 February 2017;
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, 1946 to 01 February 2017);
- Embase (OvidSP, 1974 to 01 February 2017);

- CINAHL (EBSCOHST, 1937 to 01 February 2017);
- PsycINFO (EBSCOHST, 1900 to 01 February 2017);
- ProQuest Dissertations & Theses Global (ProQuest, 1861 to 01 February 2017);
- Psychology and Behavioral Sciences Collection (EBSCOHST, 1930 to 01 February 2017);
- Web of Science Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, 1990 to 01 February 2017).

We also searched the following trial registries for ongoing trials:

- ClinicalTrials.gov ( [clinicaltrials.gov/](http://clinicaltrials.gov/)) searched on 01 February 2017;
- WHO International Clinical Trials Registry Platform (ICTRP) ( [apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)) searched on 01 February 2017;
- ISRCTN registry ( [www.isrctn.com/](http://www.isrctn.com/)) searched on 01 February 2017.

Search strategies can be found in an appendix (Appendix 1).

### Searching other resources

We handsearched reference lists of included trials in order to identify further relevant trials.

## Data collection and analysis

### Selection of studies

We selected trials according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Three review authors (PF, KM, LE) independently screened all electronically-derived citations and abstracts of papers identified by the search strategy for relevance. We excluded studies that were clearly irrelevant at this stage based on the abstract. Three review authors (PF, KM, LE) independently assessed the full texts of all potentially-relevant studies for eligibility against the criteria outlined above. We resolved disagreements by discussion, if we did not reach a consensus or if we were unsure of trial eligibility, we consulted a third review author (LE or SH). We sought further information from trial investigators if the trial report or abstract contained insufficient data to make a decision about eligibility. We used Covidence software to assess trial eligibility, which included ascertaining whether the participants had SCD or thalassaemia, if the trial addressed interventions to improve adherence to iron chelation therapy, and whether the trial was randomised or a NRSI or a CBA or an ITS study (Covidence). We recorded the reasons why potentially-relevant studies failed to meet the eligibility criteria.

### Data extraction and management

Three review authors (PF, SF, KM) extracted the data according to Cochrane guidelines (Higgins 2011a). We resolved disagreements by consensus or we consulted a fourth review author (LE). We extracted data independently for all of the trials using Covidence modified to reflect the outcomes in this review (Covidence). In addition, we used the available tables in Review Manager 5 to extract data on trial characteristics as below (RevMan 2014).

### 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

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

Adherence rates, SAEs, all-cause mortality, sustained adherence to therapy, health-related QoL, 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.

We used both full-text versions and abstracts as data sources and used one data extraction form for each unique study. Where sources did not provide sufficient information, we contacted authors for additional details.

Three review authors (PF, SF, KM) entered data and we resolved disagreements by consensus.



If NRSIs had been identified we planned to extract data according to the criteria developed for NRSIs as recommended in Chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011). In addition to the items above, for NRSIs, CBA and ITS studies we also planned to collect data 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).

### Assessment of risk of bias in included studies

Three review authors (PF, KM, SF) assessed all included trials for possible risks of bias as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c).

The assessment included information about the design, the conduct and the analysis of the trial. We assessed each criterion using Cochrane's tool for assessing the risk of bias for RCTs (classified 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 resolved disagreements on the assessment of quality of an included trial by discussion until we reached consensus or failing that by consulting a fourth review author (LE).

The only included trials were RCTs. In future updates of this review, we plan to use the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) to rate the quality of NRSIs and 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
- 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

In future updates of this review, for ITS studies we plan to 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?

### Measures of treatment effect

#### RCTs

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

For RCTs of dichotomous outcomes we recorded the number of events and the total number of participants in both the treatment and control groups and reported 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 trials have balanced treatment groups, we would have reported the Peto odds ratio (OR) with 95% CI (Deeks 2011).

There were no eligible cluster randomised trials, if such trials are included in future updates of this review, we plan to 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).

#### Non-randomised studies

There were no eligible NRSIs, if such studies are included in future updates of this review, we plan to extract and report the RR with a 95% CI for dichotomous outcomes, adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post intervention / RR pre intervention). For continuous variables we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (e.g. 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

There were no eligible ITS studies, if such studies are included in future updates, we plan to 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 plan to report the number-needed-to-treat-to-benefit (NNTB) and the number-needed-to-treat-to-harm (NNTH) with CIs.

If we are unable to report the available data in any of the formats described above, we will perform a narrative report, and if appropriate, present the data in tables.

### Unit of analysis issues

For trials with multiple treatment groups or interventions, we included subgroups that were considered relevant to the analysis. If appropriate, we combined groups to create a single pair-wise comparison. If this was not possible, we selected the most appropriate pair of interventions and excluded the others (Higgins 2011d). No trials randomised participants more than once.

There were no included cluster randomised studies or NRSIs. If these are included in future updates of this review, we plan to treat any unit of analysis issues that arise in accordance with the advice given in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

There were no included ITS studies. If these are included in future updates of this review, we plan to deal with any unit of analysis issues arising from their inclusion according to the EPOC recommendations (EPOC 2015).

### Dealing with missing data

Where we identified data as being missing or unclear in the published literature, we contacted trial authors directly. We contacted three authors for additional trial information (Antmen 2013; Badawy 2010; Elalfy 2015) and have received one response stating that the trial data were not available at this time (Badawy 2010).

We recorded the number of participants lost to follow-up for each trial. Where possible, we analysed data on an intention-to-treat (ITT) basis, but if insufficient data were available, we also presented a per protocol analyses (Higgins 2011c).

### Assessment of heterogeneity

If the clinical and methodological characteristics of individual trials were sufficiently homogeneous, we combined the data to perform a meta-analysis. We planned to analyse the data from RCTs, NRSIs, CBA and ITS studies separately, but we only included RCTs.

We assessed statistical heterogeneity of treatment effects between trials using a  $\chi^2$  test with a significance level at  $P < 0.1$ . We used the  $I^2$  statistic to quantify the degree of potential heterogeneity and classified it as moderate if  $I^2$  is greater than 50%, or considerable

if  $I^2$  is greater than 75%. We used the random-effects model as we anticipated that we would identify at least moderate clinical and methodological heterogeneity within the trials selected for inclusion. If statistical heterogeneity was considerable, we did not report the overall summary statistic. We assessed potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

### Assessment of reporting biases

No meta-analysis in this review included at least 10 trials, we therefore could not perform a formal assessment of publication bias (Sterne 2011).

### Data synthesis

If trials were sufficiently homogenous in their design, we conducted a meta-analysis according to the recommendations of Cochrane (Deeks 2011). We used the random-effects model for all analyses as we anticipated that true effects would be related but not the same for included trials. If we could not perform a meta-analysis we commented on the results as a narrative.

For RCTs where meta-analysis was feasible, we used the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. We did not have outcomes that included data from cluster-RCTs. Where heterogeneity was above 75%, and we identified a cause for the heterogeneity, we explored this with subgroup analyses. If we did not find a cause for the heterogeneity then we did not perform a meta-analysis.

If identified, we planned to analyse NRSIs or CBA studies separately. We planned to analyse outcomes with adjusted effect estimates if these were 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). For ITS studies, we would have used the effect sizes (if reported in the included studies or obtained (as described earlier)) and pooled them using the generic inverse variance method in Review Manager 5 (RevMan 2014).

### Subgroup analysis and investigation of heterogeneity

We reported results for the different types of disease separately (SCD or thalassaemia). Only one trial included participants with SCD (Vichinsky 2007).

There were insufficient data to perform some of the planned subgroup analyses. We planned to 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))
- Route of administration of iron chelating agents (oral, intravenous or subcutaneous)

### Sensitivity analysis

There were insufficient data to perform the planned sensitivity analyses. If adequate data were available, we planned to assess the robustness of our findings by performing the following sensitivity analyses according to Cochrane recommendations where appropriate (Deeks 2011).

- Including only those trials 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 used the GRADE approach to generate a 'Summary of Findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a). We used 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)
- Inconsistency (serious or very serious)
- Indirectness (serious or very serious)
- Imprecision (serious or very serious)
- Publication bias (likely or very likely)

For NRSIs or CBA or ITS studies, we planned to 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 NRSIs or CBA or ITS studies are rated initially as low quality and upgraded according to GRADE guidelines if appropriate. We planned to present outcomes for these studies in separate tables from outcomes for the results of RCTs.

We reported the following outcomes in each 'Summary of findings' table.

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

## RESULTS

### Description of studies

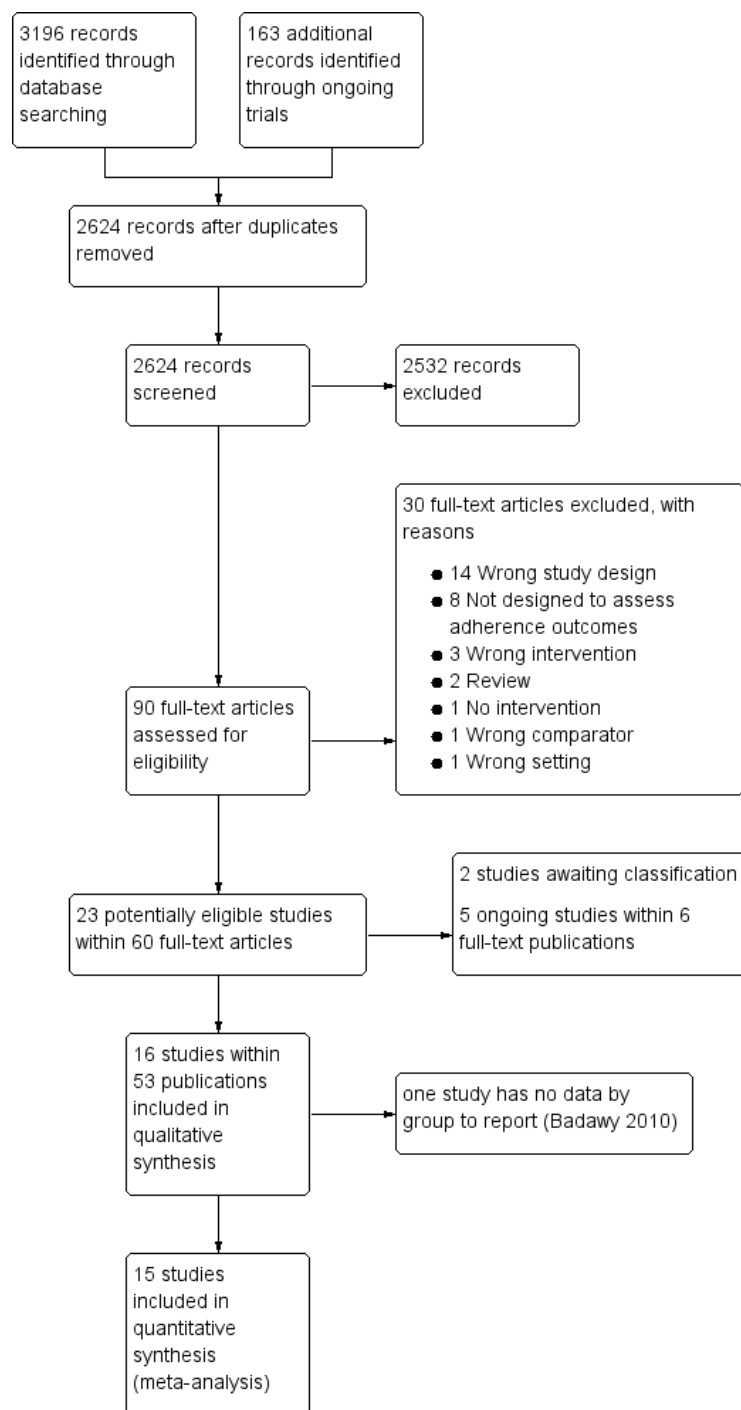
See also [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

### Results of the search

See PRISMA flow diagram ([Figure 1](#)).



**Figure 1. Study flow diagram.**



In the searches for this review we identified a total of 3359 potentially relevant references. There were 2624 references after we removed duplicates and three review authors (PF, KM and LE) excluded 2533 references on the basis of abstract and three authors (PF, KM, LE) reviewed 90 full-text articles for relevance.

We excluded 30 studies that were not relevant and identified 16 studies within 53 publications - all were RCTs (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2015; El Beshlawy 2008; Galanello 2006; Hassan 2016; Maggio 2009; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007).

We also identified five ongoing RCTs (IRCT2015101218603N2; EudraCT 2012-000353-31; Madderom 2016; NCT02173951; NCT02435212), and two studies awaiting classification (Antmen 2013; NCT00004982). We did not identify any cluster-randomised trials, NRSIs, CBA or ITS studies that met the inclusion criteria.

### Included studies

Sixteen RCTs including 1525 participants met the pre-defined inclusion criteria (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Galanello 2006; Hassan 2016; Maggio 2009; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007). Two of the included trials were abstract reports only (Badawy 2010; Olivieri 1997). One abstract did not report outcomes by intervention and therefore is not included in the quantitative reporting of the effects of interventions (Badawy 2010).

### Trial design

There were 15 RCTs of medication interventions (Aydinok 2007; Badawy 2010; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Galanello 2006; Hassan 2016; Maggio 2009; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007); while one was an RCT on medication management (Bahnasawy 2017).

Ten were multicentre trials (Calvaruso 2015; Elalfy 2015; Galanello 2006; Maggio 2009; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007) and ranged from two centres in one country (Calvaruso 2015; Elalfy 2015; Olivieri 1997) to 44 centres in multiple countries (Vichinsky 2007). Six were single-centre trials (Aydinok 2007; Bahnasawy 2017; Badawy 2010; El Beshlawy 2008; Hassan 2016; Mourad 2003).

Follow-up ranged from six months in two trials (Bahnasawy 2017; Taher 2017) to five years in two trials (Calvaruso 2015; Maggio 2009). The remainder of the trials were of 12 months duration, except in the Badawy trial, which did not report follow-up time (

Badawy 2010); and the Olivieri trial, which had 24 months follow-up (Olivieri 1997).

### Trial size

The number of participants enrolled in the trials ranged from 24 (Aydinok 2007) to 213 (Maggio 2009). Sample-size calculations were reported in eight trials (Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Maggio 2009; Pennell 2006; Pennell 2014; Tanner 2007; Vichinsky 2007).

### Setting

Trials were published between 1997 and 2017. Five were conducted in Egypt (Badawy 2010; Bahnasawy 2017; Elalfy 2015; El Beshlawy 2008; Hassan 2016); five in Italy (Calvaruso 2015; Galanello 2006; Maggio 2009; Pennell 2006; Tanner 2007); and three were international multicentre trials conducted in several countries (Pennell 2014; Taher 2017; Vichinsky 2007). One trial was conducted in each of the following countries: Turkey (Aydinok 2007); Lebanon (Mourad 2003); and Canada (Olivieri 1997).

### Participants

Fourteen trials included only participants with  $\beta$ -thalassaemia major (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Elalfy 2015; El Beshlawy 2008; Galanello 2006; Hassan 2016; Maggio 2009; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007). One trial included only participants with SCD (Vichinsky 2007); and one trial included only participants with thalassaemia intermedia (Calvaruso 2015).

The mean age ranged from 11 years (El Beshlawy 2008) to 41 years (Calvaruso 2015). Two trials only provided the minimum age of enrolment into the RCT, at least eight years old in the Badawy trial (Badawy 2010); and at least 10 years old in the Olivieri trial (Olivieri 1997).

Participants tended to be equally divided between males and females with the lowest percentage of males at 38% (Bahnasawy 2017) to a high of 66% (Elalfy 2015).

### Intervention

In this review we report the *Effects of interventions* by the various comparisons in the different trials. All trials included medication interventions except for one, which was a medication management intervention by a clinical pharmacist (Bahnasawy 2017).

The comparisons and studies included:

- **DFP versus DFO:** five trials (Badawy 2010; Calvaruso 2015; El Beshlawy 2008; Olivieri 1997; Pennell 2006);

- **DFX versus DFO:** three trials ([Hassan 2016](#); [Pennell 2014](#); [Vichinsky 2007](#));
- **DFX (film-coated tablet (FCT) versus DFX (dispersible tablet (DT)):** one trial ([Taher 2017](#));
- **DFP and DFO combined versus DFP alone:** four trials ([Aydinok 2007](#); [Badawy 2010](#); [El Beshlawy 2008](#); [Maggio 2009](#));
- **DFP and DFO combined versus DFO alone:** five trials ([Badawy 2010](#); [El Beshlawy 2008](#); [Galanello 2006](#); [Mourad 2003](#); [Tanner 2007](#));
- **DFP and DFO combined versus DFP and DFX combined:** one trial ([Elalfy 2015](#));
- **Medication management versus standard care:** one trial ([Bahnasawy 2017](#)).

### Outcomes

Outcomes varied across trials depending on the objectives. All trials measured adherence, although this was usually as a secondary, rather than a primary outcome. Reduction in serum ferritin or LIC were the primary outcomes in most trials; however, in three trials the primary outcome was myocardial T2\* MRI results ([Pennell 2006](#); [Pennell 2014](#); [Tanner 2007](#)) and in one trial was overall safety ([Taher 2017](#)). Safety (including both SAEs and AEs) was included as a secondary outcome in all trials. QoL was reported in three trials ([Aydinok 2007](#); [Bahnasawy 2017](#); [Elalfy 2015](#)).

### Source

Four trials identified non-profit organisations as their source of support, including universities, foundations and societies ([Badawy 2010](#); [Calvaruso 2015](#); [Elalfy 2015](#); [Maggio 2009](#)).

Five trials identified industry sponsorships ([Galanello 2006](#); [Pennell 2006](#); [Pennell 2014](#); [Taher 2017](#); [Vichinsky 2007](#)). Six trials did not state their source of funding ([Aydinok 2007](#); [Bahnasawy](#)

[2017](#); [El Beshlawy 2008](#); [Hassan 2016](#); [Mourad 2003](#); [Olivieri 1997](#)); but of these, three may have had industry funding. In one trial, drugs were supplied by the manufacturer ([Aydinok 2007](#)); one trial was halted by the manufacturer ([Olivieri 1997](#)); and one trial included industry employees as authors ([El Beshlawy 2008](#)). One trial had a mix of non-profit and industry funding ([Tanner 2007](#)).

### Excluded studies

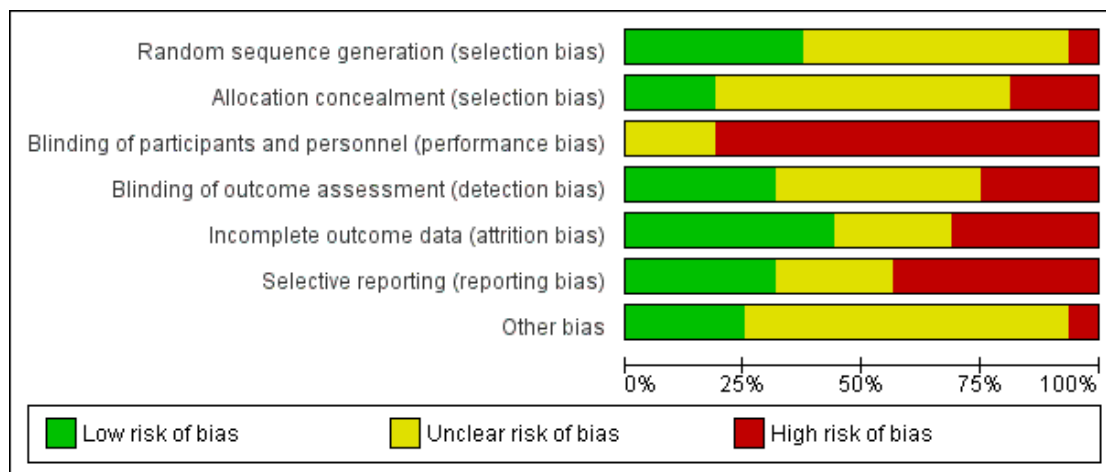
We excluded 30 trials:

- in 14 trials the trial design did not meet the inclusion criteria ([Abu 2015](#); [Al Kloub 2014](#); [Al Kloub 2014a](#); [Al Refaie 1995](#); [Alvarez 2009](#); [Kidson Gerber 2008](#); [Kolnagou 2008](#); [Leonard 2014](#); [NCT02133560](#); [NCT02466555](#); [Pakbaz 2004](#); [Pakbaz 2005](#); [Porter 2009](#); [Porter 2012](#));
- eight trials were not designed to assess adherence ([Berkovitch 1995](#); [Chakrabarti 2013](#); [NCT01709032](#); [NCT01825512](#); [Vichinsky 2005](#); [Vichinsky 2008](#); [Waheed 2014](#); [Yarali 2006](#));
- three trials assessed the wrong intervention ([Armstrong 2011](#), [Belgrave 1989](#); [Gomber 2004](#));
- one trial had no interventions ([Bala 2014](#));
- one trial had a wrong comparator ([Mazzone 2009](#));
- one trial was in the wrong setting ([Daar 2010](#));
- two were reviews ([Loiselle 2016](#); [Walsh 2014](#)).

### Risk of bias in included studies

Refer to the figures section of the review for visual representations of the assessments of risk of bias across all trials and for each item in the included trials ([Figure 2](#); [Figure 3](#)). See the risk of bias section in the [Characteristics of included studies](#) section for further information about the bias identified within individual trials.

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



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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aydinok 2007	+	-	-	?	-	+	?
Badawy 2010	?	?	-	?	-	-	?
Bahnasawy 2017	?	?	-	-	-	-	?
Calvaruso 2015	+	+	-	+	+	+	?
Elalfy 2015	+	+	-	+	+	?	?
El Beshlawy 2008	?	?	-	?	-	-	?
Galanello 2006	?	?	?	?	+	?	+
Hassan 2016	?	?	-	-	+	-	?
Maggio 2009	+	+	-	+	?	+	?
Mourad 2003	?	?	?	?	+	-	+
Olivieri 1997	-	?	-	?	-	+	?
Pennell 2006	?	?	-	+	+	-	-
Pennell 2014	+	?	-	+	?	?	+
Taher 2017	?	-	-	-	?	-	?
Tanner 2007	?	-	?	?	?	+	+
Vichinsky 2007	+	?	-	-	+	?	?

## Allocation

### Random sequence generation

We considered six trials to be at a low risk of bias for random sequence generation as randomisation was clearly described and done centrally, in permuted blocks, or computer-generated (Aydinok 2007; Calvaruso 2015; Elalfy 2015; Maggio 2009; Pennell 2014; Vichinsky 2007).

We considered nine trials to be at an unclear risk of bias. Although one trial used permuted blocks there were several imbalances in baseline characteristics between groups (Hassan 2016). We judged the remaining eight trials to have an unclear risk of bias as there was no description of randomisation and the report only stated that participants were randomised (Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Galanello 2006; Mourad 2003; Pennell 2006; Taher 2017; Tanner 2007).

We considered one trial to be at a high risk of bias as participants were “assigned” to treatment groups by a research pharmacist and there was no description of how it was done (Olivieri 1997).

### Allocation concealment (selection bias)

We considered three trials to be at low risk for selection bias as participants were allocated by telephone contact from a co-ordinating centre (Calvaruso 2015; Elalfy 2015; Maggio 2009).

We considered 10 trials to be at an unclear risk as there was no description of how allocation was concealed (Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Galanello 2006; Hassan 2016; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Vichinsky 2007).

We considered three trials to be at a high risk for selection bias as there was no allocation concealment (Aydinok 2007; Taher 2017; Tanner 2007).

## Blinding

### Blinding of participants and personnel (performance bias)

We considered three trials to be at an unclear risk for performance bias as there was no description of blinding (Galanello 2006; Mourad 2003; Tanner 2007).

We considered 13 trials to be at a high risk for performance bias. Trials were either open label, did not mention blinding, or blinding was difficult due to type of treatment: a subcutaneous injection compared to an oral intervention or combination of both (Aydinok 2007; Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Calvaruso 2015; Elalfy 2015; Hassan 2016; Maggio 2009;

Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Vichinsky 2007).

### Blinding of outcome assessment (detection bias)

We considered five trials to be at a low risk of detection bias for all outcomes as data management and analysis were carried out by assessors who were blinded to interventions (Calvaruso 2015; Elalfy 2015; Maggio 2009; Pennell 2006; Pennell 2014).

We considered seven trials to be at an unclear risk of detection bias for all outcomes except mortality as there was no mention of blinding (Aydinok 2007; Badawy 2010; El Beshlawy 2008; Galanello 2006; Mourad 2003; Olivieri 1997; Tanner 2007).

We considered four trials to be at a high risk of detection bias as there was no description of blinding of outcome assessment and it appears that investigators who were not blinded were also involved in outcome assessment (Bahnasawy 2017; Hassan 2016; Taher 2017; Vichinsky 2007).

### Incomplete outcome data

We considered seven trials to be at a low risk for attrition bias as all outcomes were reported and either no participants or few participants were lost to follow-up and flow of participants was reported (Calvaruso 2015; Elalfy 2015; Galanello 2006; Hassan 2016; Mourad 2003; Pennell 2006; Vichinsky 2007).

We considered four trials to be at an unclear risk of attrition bias as there was no indication of the number of participants included in the different outcome analyses; there was substantial attrition towards the end of the trial, a per protocol analysis was conducted for some outcomes; or there was high attrition or vague reporting with no specific results (Maggio 2009; Pennell 2014; Taher 2017; Tanner 2007).

We considered the rest of the trials to be at a high risk for attrition bias as there was no data on the flow and number of participants completing the trial; no participant numbers on adverse events or compliance; no comparative data reported; per protocol analysis only; or large attrition bias in outcome analysis (Aydinok 2007; Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Olivieri 1997).

### Selective reporting

We considered five trials to be at a low risk of reporting bias as all identified outcomes were reported (Aydinok 2007; Calvaruso 2015; Maggio 2009; Olivieri 1997; Tanner 2007).

We considered four trials to be at an unclear risk of reporting bias because of either: minimal reporting of participant satisfaction and compliance; or no report of compliance with DFP; or unclear and

selective reporting of adverse events (Elalfy 2015; Galanello 2006; Pennell 2014; Vichinsky 2007).

We considered seven trials to be at a high risk of reporting bias due to: the incomplete reporting of adverse events or a lack of reporting of adverse events by treatment groups; or a lack of detailed or incomplete reporting of compliance and serum ferritin and LIC; or non-reporting of some pre-specified outcomes (Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Hassan 2016; Mourad 2003; Pennell 2006; Taher 2017).

### Other potential sources of bias

We considered four trials to be at a low risk as no other potential sources of bias were identified (Galanello 2006; Mourad 2003; Pennell 2014; Tanner 2007).

We considered 11 trials to be at an unclear risk of other bias for various reasons including: baseline imbalances; abstract reports with insufficient details; no comparative numbers in control group; incomplete reporting of AEs; dose amendments after the start of the trial (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Hassan 2016; Maggio 2009; Olivieri 1997; Taher 2017; Vichinsky 2007).

We considered one trial to be at a high risk of other sources of bias due to a serious imbalance in baseline characteristics of participants, particularly serum ferritin levels (Pennell 2006).

### Effects of interventions

See: [Summary of findings for the main comparison](#) DFP compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 2](#) DFX compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 3](#) DFX film-coated tablet compared to DFX dispersible tablet for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 4](#) DFP and DFO compared to DFP for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 5](#) DFP and DFO compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 6](#) DFP and DFO compared to DFP and DFX for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; [Summary of findings 7](#) Medication management compared to standard care for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. Results are presented for each of the main comparisons.

The main focus of our review is on compliance and effects of compliance (or non-compliance) on participant outcomes. For more detailed estimates of effectiveness of different iron chelators please refer to another Cochrane Review (Fisher 2013).

One abstract of a trial that included three review comparisons (DFP versus DFO; combination DFP and DFO versus DFP; combination DFP and DFO versus DFO) did not report any outcomes by intervention group and did not include counts of events (i.e. adverse events); therefore we did not include this trial in the quantitative analysis (Badawy 2010). Thus we have included 15 trials within the quantitative analysis.

See [Table 1](#) and also the outcomes section in the [Characteristics of included studies](#) section for summary information on results and how adherence was measured in the individual trials. Adherence rates were mostly measured by pill or vial count (either automated or manual).

The quality of the evidence has been graded for those outcomes included in the summary of findings table. For the definitions of these gradings, please refer to the summary of findings tables ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); [Summary of findings 6](#); [Summary of findings 7](#)).

### DFP (deferiprone) alone versus DFO (deferioxamine) alone

Four trials of thalassaemia met the inclusion criteria for this comparison (Calvaruso 2015; El Beshlawy 2008; Olivieri 1997; Pennell 2006). See [Summary of findings for the main comparison](#).

### Primary outcomes

#### 1. Adherence to iron chelation therapy rates

We are uncertain whether oral DFP increases adherence to iron chelation therapy more than subcutaneous DFO (very low-quality evidence). Results could not be combined due to both a lack of data to report as well as considerable heterogeneity between comparisons ( $I^2 = 99\%$ ) (Analysis 1.1). We identified the age of participants and differences in the medication regimens as possible explanations for heterogeneity. We provide a narrative review of the data on compliance below.

- Calvaruso 2015: compliance with DFP: 85% (47 participants) versus compliance with DFO: 76% (41 participants).
- El Beshlawy 2008: “four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period”.
- Olivieri 1997: compliance with DFP:  $94.9\% \pm 1.1\%$  (19 participants) versus compliance with DFO:  $71.6\% \pm 3.9\%$  (18 participants).
- Pennell 2006: compliance with DFP:  $94\% \pm 5.3\%$  (29 participants) versus compliance with DFO:  $93\% \pm 9.7\%$  (32 participants).

## 2. Serious adverse events (SAEs)

Two trials reported this outcome (Calvaruso 2015; Pennell 2006). One trial reported on the risk of developing agranulocytosis: we are uncertain if switching to oral DFP increases the risk of agranulocytosis compared to subcutaneous DFO, RR 7.88 (95% CI 0.18 to 352.39) (one trial; 88 participants; very low-quality evidence) (Calvaruso 2015) (Analysis 1.2). No SAEs occurred in the second trial (Pennell 2006).

## 3. All-cause mortality

Two trials reported this outcome (Calvaruso 2015; Pennell 2006). Oral DFP may have little or no difference on mortality compared to subcutaneous DFO, RR 0.44 (95% CI 0.12 to 1.63) (88 participants; one trial; low-quality evidence) (Calvaruso 2015) (Analysis 1.3). No deaths occurred in the second trial (Pennell 2006).

## Secondary outcomes

### 1. Sustained adherence to therapy (measured for a minimum of six months)

All trials reported more than six months follow-up, sustained adherence is reported in the primary outcome (adherence to iron chelation therapy rates), as only end-of-trial adherence numbers were provided.

### 2. Health-related quality of life (QoL)

No trials measured QoL.

### 3. Iron overload

One trial reported the proportion of participants with iron overload (Calvaruso 2015). We are uncertain if DFP reduces iron overload compared to DFO: iron levels greater or equal to 800 (µg/L), RR 1.31 (95% CI 0.49 to 3.48) (one trial; 38 participants; very low quality evidence) (Analysis 1.4).

### 4. Organ damage

One trial reported the proportion of participants with organ damage (Calvaruso 2015). We are uncertain if DFP increases the risk of liver damage compared to DFO, RR 4.36 (95% CI 0.53 to 35.82) (one trial; 88 participants; very low-quality evidence) (Analysis 1.5).

## 5. Other adverse events (AEs) related to iron chelation

Three trials reported this outcome (Calvaruso 2015; El Beshlawy 2008; Pennell 2006). In people with thalassaemia taking DFP, we are uncertain if there is a difference in the risk of AEs compared to people taking DFO (Analysis 1.6).

- Risk of leukopenia: RR 3.94 (99% CI 0.44 to 35.50) (three trials; 192 participants; very low-quality evidence) (Calvaruso 2015; El Beshlawy 2008; Pennell 2006).

- Risk of pain or swelling in joints: RR 3.38 (99% CI 0.54 to 21.31) (three trials; 192 participants; very low-quality evidence) (Calvaruso 2015; El Beshlawy 2008; Pennell 2006).

- Risk of nausea or vomiting: RR 13.68 (99% CI 0.99 to 188.88) (two trials; 132 participants; very low-quality evidence) (Calvaruso 2015; El Beshlawy 2008).

- Risk of increased liver transaminase: RR 1.10 (99% CI 0.03 to 38.47) (one trial; 44 participants; very low-quality evidence) (El Beshlawy 2008).

- Local reactions at infusions site: RR 0.17 (99% CI 0.00 to 9.12) (one trial; 88 participants; very low-quality evidence) (Calvaruso 2015).

In all trials we downgraded the quality of evidence by one for risk of bias (due to high or unclear risk of bias in several domains) and in one trial we downgraded by two due to imprecision, the effect estimates have wide CIs (Calvaruso 2015).

## DFX (deferiasirox) alone versus DFO (deferroxamine) alone

Three trials met the inclusion criteria for this comparison; two in thalassaemia (Hassan 2016; Pennell 2014); and one in SCD (Vichinsky 2007). See Summary of findings 2.

## Primary outcomes

### 1. Adherence to iron chelation therapy rates

All three trials reported on this outcome. Only one trial reported data in a format that could be incorporated into the analysis (Pennell 2014). We are uncertain if DFX increases the rate of adherence compared to people taking DFO, MD -1.40 (95% CI -3.66 to 0.86) (one trial; 197 participants; very-low quality evidence) (Analysis 2.1).

Regarding the remaining two trials:

- Hassan 2016 stated that “throughout the study, all patients were compliant with the prescribed doses, and no discontinuation of drugs or drop-out of follow-up occurred.”

- Vichinsky 2007 reported that “the ratios of the administered to intended doses of therapy were high (1.16 for deferiasirox and 0.97 for deferroxamine), indicating high adherence to the prescribed treatment regimens.”



## 2. Serious adverse events (SAEs)

All three trials reported the effect on disease-related SAEs (Hassan 2016; Pennell 2014; Vichinsky 2007); two in thalassaemia (Hassan 2016; Pennell 2014), and one in SCD (Vichinsky 2007).

We are uncertain whether DFX decreases risk of disease-related SAEs in thalassaemia compared to DFO, RR 0.95 (95% CI 0.41 to 2.17) (two trials; 247 participants; very low-quality evidence) (Analysis 2.2).

We are uncertain whether DFX decreases the risk of SCD-related pain crisis, RR 1.05 (95% CI 0.68 to 1.62) (one trial; 195 participants; very low-quality evidence); or other SCD-related SAEs compared to DFO, RR 1.08 (95% CI 0.77 to 1.51) (one trial; 195 participants; very low-quality evidence) (Analysis 2.2).

## 3. All-cause mortality

Two trials report mortality (Hassan 2016; Pennell 2014). We are uncertain whether DFX decreases the risk of mortality in people with thalassaemia compared to DFO, RR 0.96 (95% CI 0.06 to 15.06) (two trials; 240 participants; very low-quality evidence) (Analysis 2.3).

## Secondary outcomes

### 1. Sustained adherence to therapy (measured for a minimum of six months)

All trials reported more than six months follow-up, sustained adherence is reported in the primary outcome (adherence to iron chelation therapy rates), as only end-of-trial adherence numbers were provided.

### 2. Health-related quality of life (QoL)

No trials measured quality of life.

### 3. Iron overload

In people with thalassaemia, we are uncertain whether DFX reduces the proportion of participants with serum ferritin of 1500 (µg/l) or higher, RR 1.18 (95% CI 0.63 to 2.20) (one trial; 60 participants; very low-quality evidence) (Hassan 2016) (Analysis 2.4). Furthermore, we are uncertain whether DFX reduces the proportion of participants with severe LIC (15 mg Fe/g dw or higher), RR 1.00 (95% CI 0.83 to 1.20); or myocardial T2\* < 10 ms, RR 1.10 (95% CI 0.72 to 1.70) (one trial; 172 participants; very low-quality evidence)\* (Pennell 2014) (Analysis 2.4).

\*LIC and myocardial T2\* analyses from Pennell 2014 were based on the per protocol population.

In people with SCD, Vichinsky reported LIC mean changes from baseline and no data on proportion of participants with end-of-trial iron overload (Vichinsky 2007).

## 4. Organ damage

No trial reported any other organ damage.

## 5. Other adverse events (AEs) related to iron chelation

In people with thalassaemia taking DFX, we are uncertain if there is a difference in the risk of iron chelation therapy-related AEs compared to people taking DFO (Analysis 2.5).

- Risk of total iron chelation therapy-related AE: RR 1.15 (95% CI 0.76 to 1.73); (one trial; 187 participants; very low-quality evidence) (Pennell 2014).

- Risk of gastrointestinal upset: RR 3.00 (95% CI 0.66 to 13.69); (one trial; 60 participants; very low-quality evidence) (Hassan 2016).

- Risk of rash: RR 3.05 (95% CI 0.98 to 9.47); (two trials; 247 participants; very low-quality evidence) (Hassan 2016; Pennell 2014).

- Risk of increased blood creatinine: RR 3.79 (95% CI 0.83 to 17.38); (one trial; 187 participants; very low-quality evidence) (Pennell 2014).

- Risk of proteinuria: RR 2.21 (95% CI 0.59 to 8.29); (one trial; 187 participants; very low-quality evidence) (Pennell 2014).

- Risk of increased ALT: RR 5.69 (95% CI 0.70 to 46.33); (one trial; 187 participants; very low-quality evidence); (Pennell 2014).

- Risk of increased AST: RR 5.69 (95% CI 0.70 to 46.33); (one trial; 187 participants; very low-quality evidence); (Pennell 2014).

- Risk of diarrhoea: RR 5.69 (95% CI 0.70 to 46.33); (one trial; 187 participants; very low-quality evidence); (Pennell 2014).

- Risk of vomiting: RR 6.64 (95% CI 0.35 to 126.78); (one trial; 187 participants; very low-quality evidence); (Pennell 2014).

In people with thalassaemia, we are uncertain whether DFX reduces the incidence of total AEs as compared to DFO, RR 0.89 (95% CI 0.75 to 1.07) (one trial; 187 participants; very low-quality evidence) (Pennell 2014) (Analysis 2.6). We downgraded the quality of evidence either by two due to high or uncertain risk of bias in several domains, or by one due to imprecision as CIs are wide and only one trial with data in comparison, or both.

In people with SCD, DFX compared to DFO, may increase slightly the risk of abdominal pain, RR 1.91 (99% CI 0.80 to 4.58); the risk of diarrhoea, RR 4.14 (99% CI 0.90 to 18.92); and the risk of nausea or vomiting, RR 1.63 (99% CI 0.90 to 2.94) (one trial; 195 participants; low-quality evidence) (Vichinsky 2007) (Analysis 2.7). We are uncertain if DFX compared to DFO increases the risk of an increase in ALT, RR 5.29 (99% CI 0.12 to 232.98) or the risk of pain or swelling in joints, RR 1.06 (99% CI 0.41 to 2.76) (one trial; 195 participants; very low-quality evidence) (Vichinsky 2007) (Analysis 2.7). We downgraded the quality of evidence either by two due to high or uncertain risk of bias in

several domains, or by one due to imprecision as CIs are wide and only one trial with data in comparison, or both.

### **DFX film-coated Tablet (FCT) versus DFX (deferasirox) dispersible tablet (DT)**

One trial in thalassaemia met the inclusion criteria for this comparison ([Taher 2017](#)). See [Summary of findings 3](#).

#### **Primary outcomes**

##### **Adherence to iron chelation therapy rates**

DFX FCT may have little or no difference on adherence as compared to DFX DT, RR 1.10 (95% CI 0.99 to 1.22) (one trial; 173 participants; low-quality evidence) (Analysis 3.1).

##### **Serious adverse events (SAEs)**

We are uncertain if DFX FCT increases SAEs as compared to DFX DT, RR 1.22 (95% CI 0.62 to 2.37) (one trial; 173 participants; very low-quality evidence) (Analysis 3.2).

##### **All-cause mortality**

We are uncertain if DFX FCT increases all-cause mortality as compared to DFX DT, RR 2.97 (95% CI 0.12 to 71.81) (one trial; 173 participants; very low-quality evidence) (Analysis 3.3).

#### **Secondary outcomes**

##### **1. Sustained adherence to therapy**

This trial reported more than six months follow-up, sustained adherence is reported in the primary outcome (adherence to iron chelation therapy rates), as only end of trial adherence numbers were provided.

##### **2. Health-related quality of life (QoL)**

This outcome was not measured with a validated instrument.

##### **3. Iron overload**

The trial did not report the proportion of participants with iron overload at the end of the trial.

#### **4. Organ damage**

We are uncertain if DFX FCT increases the incidence of renal events as compared to DFX DT, RR 1.25 (95% CI 0.83 to 1.91) (one trial; 173 participants; very low-quality evidence) (Analysis 3.4).

#### **5. Other adverse events (AEs) related to iron chelation**

DFX FCT, compared to DFX DT, may improve slightly the incidence of all chelation-related AEs, RR 0.75 (99% CI 0.52 to 1.08); and the incidence of vomiting, RR 0.28 (99% CI 0.07 to 1.15) (one trial; 173 participants; low-quality evidence) (Analysis 3.5).

We are uncertain if DFX FCT, compared to DFX DT, improves: the risk of diarrhoea, RR 0.70 (99% CI 0.29 to 1.70); the incidence of abdominal pain, RR 0.49 (99% CI 0.16 to 1.52); the incidence of nausea, RR 0.72 (99% CI 0.23 to 2.23) or increases urine protein/urine creatinine ratio, RR 1.65 (99% CI 0.60 to 4.54) (one trial; 173 participants; very low-quality evidence) (Analysis 3.5).

We downgraded the quality of evidence by either two for risk of bias due to high or unclear risk of bias in all domains or by one for imprecision due to wide confidence intervals, or both.

### **DFP (deferiprone) and DFO (deferoxamine) combination therapy versus DFP (deferiprone) alone**

Three trials in thalassaemia met the inclusion criteria for this comparison ([Aydinok 2007](#); [El Beshlawy 2008](#); [Maggio 2009](#)). See [Summary of findings 4](#).

#### **Primary outcomes**

##### **1. Adherence to iron chelation therapy rates**

All trials reported on this outcome. We are uncertain if DFP and DFO increases adherence compared to DFP alone (very low-quality evidence).

- [Aydinok 2007](#): "Compliance was generally excellent during the entire study period. There was only one patient in the DFP treatment arm who missed more than one chelation dose per week because of problems with swallowing."

- [El Beshlawy 2008](#): "four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period."

- [Maggio 2009](#): "In the sequential DFP-DFO group, compliance was 92.7% (SD  $\pm$  15.2%; range 37-100%) with DFP treatment and 70.6% (SD  $\pm$  24.1%; range 25-100%) with DFO treatment (105 participants). Compliance with DFP was 93.6% (SD  $\pm$  9.7%; range 56-100%) in the DFP-alone patients (108 participants)."

## 2. Serious adverse events (SAEs)

Only one trial reported this outcome (Maggio 2009). In people with thalassaemia, combination therapy with DFP and DFO may have little or no difference on the incidence of SAEs as compared to DFP alone, RR 0.15 (95% CI 0.01 to 2.81) (one trial; 213 participants; low-quality evidence) (Maggio 2009) (Analysis 4.1).

## 3. All-cause mortality

Two trials reported on this outcome (Aydinok 2007; Maggio 2009). We are uncertain if combination therapy with DFP and DFO decreases mortality as compared to DFP alone, RR 0.77 (95% CI 0.18 to 3.35) (two trials; 237 participants; very low-quality evidence) (Analysis 4.2).

## Secondary outcomes

### 1. Sustained adherence to therapy

Sustained adherence is reported under the primary outcome (adherence to iron chelation rates), as all trials are longer than six months and end-of-trial adherence is reported.

### 2. Health-related quality of life (QoL)

One trial assessed QoL, but did not use a validated questionnaire (Aydinok 2007).

### 3. Iron overload

No trial reported the proportion of participants with iron overload.

### 4. Organ damage

No trial reported the proportion of participants with organ damage.

### 5. Other adverse events (AEs) related to iron chelation

All three trials reported AEs. We are uncertain if combination DFP and DFO reduces the incidence of adverse events compared to DFP alone in people with thalassaemia (Analysis 4.3).

- Risk of leukopenia, neutropenia or agranulocytosis (or a combination of): RR 1.15 (99% CI 0.50 to 2.62) (three trials; 280 participants; very low-quality evidence) (Aydinok 2007; El Beshlawy 2008; Maggio 2009).
- Risk of pain or swelling in joints: RR 0.76 (99% CI 0.31 to 1.91) (two trials; 256 participants; very low-quality evidence) (El Beshlawy 2008; Maggio 2009).
- Risk of increased liver transaminase: RR 1.02 (99% CI 0.52 to 1.98) (two trials; 256 participants; very low-quality evidence) (El Beshlawy 2008; Maggio 2009).

- Risk of nausea or vomiting: RR 0.55 (99% CI 0.13 to 2.23) (one trial; 43 participants; very low-quality evidence) (El Beshlawy 2008).

One trial reported on this outcome (Maggio 2009). Combination therapy with DFP and DFO may have little or no difference on the risk of gastrointestinal disorders as compared to DFP alone: RR 0.45 (95% CI 0.15 to 1.37) (one trial; 213 participants; low-quality evidence) (Analysis 4.3).

We downgraded the quality of evidence by either two for risk of bias due to high or unclear risk of bias in several domains in all trials, or by one due to imprecision, the effect estimates have wide confidence intervals, or both.

## DFP (deferiprone) and DFO (deferoxamine) combination therapy versus DFO (deferoxamine) alone

Four trials in thalassaemia met the inclusion criteria for this comparison (El Beshlawy 2008; Galanello 2006; Mourad 2003; Tanner 2007). See [Summary of findings 5](#).

## Primary outcomes

### 1. Adherence to iron chelation therapy rates

In people with thalassaemia, combined therapy with DFP and DFO versus DFO alone, may have little or no difference in adherence rates (low-quality evidence). We could not combine any data for an effect estimate.

- El Beshlawy 2008: "four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period".
- Galanello 2006: DFP/DFO: DFO: 96.1 ± 5.0 (29 participants); DFP compliance was not reported; DFO: 95.7 ± 5.7 (30 participants).
- Mourad 2003: "In patients receiving the combined therapy, compliance was excellent (arbitrarily defined as taking > 90% of the recommended doses) in 10 patients and good (75% to 90% of recommended doses) in one patient, as assessed by the patient's history, parental evidence and usage of tablets provided in just sufficient quantities between check-up visits. In patients receiving DFX alone, compliance was considered to be excellent in 11 patients and good in three patients, as assessed mainly by counting the vials given to, and returned by, the patients".
- Tanner 2007: "Compliance with deferoxamine was similar in both groups (combined 91.4 ± 2.7% versus deferoxamine 92.6 ± 2.7%; P = 0.7). Compliance with deferiprone was less than compliance with placebo (82.4 ± 18.1% versus 89.8 ± 7.2%; P = 0.04)".

## 2. Serious adverse events (SAEs)

Three trials reported SAEs (Galanello 2006; Mourad 2003; Tanner 2007). In people with thalassaemia, combined therapy with DFP and DFO versus DFO alone, may have little or no difference in SAEs (low-quality evidence). No SAEs occurred in the three trials.

## 3. All-cause mortality

Only one trial reported on this outcome and no deaths occurred (Tanner 2007). Combined therapy with DFP and DFO versus DFO alone, may have little or no difference in mortality (one trial; 65 participants; low-quality evidence).

## Secondary outcome

### 1. Sustained adherence to therapy

All trials reported more than six months follow-up, sustained adherence is reported in the primary outcome (adherence to iron chelation therapy rates), as only end-of-trial adherence numbers were provided.

### 2. Health-related quality of life (QoL)

No trials measured QoL.

### 3. Iron overload

No trials reported the proportion of participants with iron overload.

### 4. Organ damage

No trials reported the proportion of participants with organ damage.

### 5. Other adverse events (AEs) related to iron chelation

All four trials reported some AEs. We are uncertain if DFP combined with DFO reduces other chelation-related AEs compared to DFO alone in people with thalassaemia (Analysis 5.1).

- Risk of leukopenia, neutropenia or agranulocytosis (or a combination of): RR 1.18 (99% CI 0.09 to 15.37) (three trials; 169 participants; very low-quality evidence) (El Beshlawy 2008; Galanello 2006; Tanner 2007).
- Risk of pain or swelling in joints: RR 2.39 (99% CI 0.18 to 32.31) (three trials; 135 participants; very low-quality evidence  $I^2 = 66\%$ ) (El Beshlawy 2008; Mourad 2003; Tanner 2007).
- Risk of increased liver transaminase: RR 3.46 (99% CI 0.45 to 26.62) (two trials; 104 participants; very low-quality evidence) (El Beshlawy 2008; Galanello 2006).

- Risk of nausea or vomiting: RR 3.81 (99% CI 0.84 to 17.36) (four trials; 194 participants; very low-quality evidence) (El Beshlawy 2008; Galanello 2006; Mourad 2003; Tanner 2007).

- Risk of local reactions at infusion site: RR 0.18 (99% CI 0.01 to 3.56) (two trials; 90 participants; very low-quality evidence) (Mourad 2003; Tanner 2007).

We downgraded the quality of evidence by two for risk of bias due to high or unclear risk of bias in several domains in all trials and by one due to imprecision, the effect estimates have wide CIs.

## Combination DFP (deferiprone) and DFO (deferoxamine) versus combination DFP (deferiprone) and DFX (deferasirox)

One trial in thalassaemia met the inclusion criteria for this comparison (Elalfy 2015). See [Summary of findings 6](#).

## Primary outcomes

### 1. Adherence to iron chelation therapy rates

In children with thalassaemia, combination therapy with DFP and DFX may improve adherence to iron chelation therapy compared to combination therapy with DFP and DFO, RR 0.84 (95% CI 0.72 to 0.99) (one trial; 96 participants; low-quality evidence) (Analysis 6.1).

### 2. Serious adverse events (SAEs)

In children with thalassaemia, we are uncertain if combination therapy with DFP and DFX decreases the incidence of SAEs compared to combination therapy with DFP and DFO, RR 1.00 (95% CI 0.06 to 15.53) (one trial; 96 participants; very low-quality evidence) (Analysis 6.2).

### 3. All-cause mortality

In children with thalassaemia, combination therapy with DFP and DFX may make little or no difference in mortality compared to combination therapy with DFP and DFO. There were no deaths in the trial (one trial; 96 participants; low-quality evidence).

## Secondary outcomes

### 1. Sustained adherence to therapy

The trial reported more than six months follow-up, sustained adherence is reported in the primary outcome (adherence to iron chelation therapy rates), as only end-of-trial adherence numbers were provided.

## 2. Health-related quality of life (QoL)

In children with thalassaemia we are unclear if combination therapy with DFP and DFX improves QoL compared to combination therapy with DFP and DFO (very low-quality evidence). Authors state that “significant improvement in quality of life was observed in both groups at study end compared to baseline”; no comparative data were provided.

## 3. Iron overload

Proportion of participants with iron overload was not reported.

## 4. Organ damage

In children with thalassaemia, combination therapy with DFP and DFX as compared to DFP and DFO may have little or no difference in the incidence of increased creatinine, RR 3.00 (99% CI 0.16 to 56.04) (one trial; 96 participants; low-quality evidence) (Analysis 6.4).

## 5. Other adverse events (AEs) related to iron chelation

In children with thalassaemia, we are unclear if combination therapy with DFP and DFX as compared to DFP and DFO reduces the incidence of AEs (one trial; 96 participants; very low-quality evidence) (Analysis 6.5).

- Total drug-related AEs: RR 1.08 (99% CI 0.68 to 1.71).
- Risk of leukopenia, neutropenia, or agranulocytosis: RR 1.67 (99% CI 0.27 to 10.14).
- Risk of pain or swelling in joints: RR 0.89 (99% CI 0.29 to 2.77).
- Gastrointestinal problems: RR 0.60 (99% CI 0.18 to 2.04).
- Liver transaminase increased: RR 1.33 (99% CI 0.20 to 8.88).
- Skin rash: RR 5.00 (99% CI 0.10 to 261.34).

We downgraded the quality of evidence by one for risk of bias as there was a high or unclear risk of bias in three domains; by one for indirectness, as the trial was conducted in children aged 10 to 18 with years with severe iron overload; and by one due to imprecision, the effect estimates have wide CIs.

## Medication management versus standard care

One trial in thalassaemia met the inclusion criteria for this comparison (Bahnasawy 2017). See [Summary of findings 7](#).

## Primary outcomes

### 1. Adherence to iron chelation therapy rates

Adherence was only reported in the intervention group and not in the control group.

### 2. Serious adverse events (SAEs)

SAEs were not reported.

### 3. All-cause mortality

All-cause mortality was not reported.

## Secondary outcomes

### 1. Sustained adherence to therapy

Adherence was only reported in the intervention group and not in the control group.

### 2. Health-related quality of life (QoL)

We are uncertain if medication management improves health-related QoL: PedsQLTM HRQoL total score median (IQR): test group: 63.51 (51.75 to 84.54); control group: 49.84 (41.9 to 60.81) (one trial; 48 participants; very low-quality evidence).

### 3. Iron overload

Proportion of participants with iron overload was not reported.

### 4. Organ damage

Proportion of participants with organ damage was not reported.

### 5. Other adverse events (AEs) related to iron chelation

AEs were not reported.

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

DFX compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFX <b>Comparison:</b> DFO						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFO	Risk with DFX				
Adherence to iron chelation therapy (per cent, SD)	The mean adherence to iron chelation therapy (per cent, SD) was 0	MD 1.4 lower (3.66 lower to 0.86 higher)	-	197 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	Narrative report of adherence for 2 trials as either no or incompatible data to enable comparisons
SAEs -thalassaemia-related SAEs	Study population		-	247 (2 RCTs)	⊕○○○ VERY LOW <sup>12</sup>	There were no SAEs to report in one trial so no estimate of effect
	see comment	see comment				
SAEs - SCD-related SAEs	Study population		RR 1.08 (95%CI 0.77 to 1.51)	195 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	
	429 per 1000	463 per 1000 (330 to 647)				
Incidence of SCD-related SAEs -pain crisis	Study population		RR 1.05 (95%CI 0.68 to 1.62)	195 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	
	317 per 1000	333 per 1000 (216 to 514)				
All-cause mortality (thalassaemia)	Study population		RR 0.96 (95%CI 0.06 to 15.06)	240 (2 RCTs)	⊕○○○ VERY LOW <sup>12</sup>	

	8 per 1000	8 per 1000 (1 to 128)				
Sustained adherence - not measured	-	-	-	-	-	Sustained adherence is reported as adherence as all trials were longer than 6 months and only end of trial adherence reported
Quality of life - not reported	-	-	-	-	-	
<p><b>*The risk in the intervention group</b> (and its 95% CI) is based on the assumed risk in the comparison group and the <b>relative effect</b> of the intervention (and its 95% CI).</p> <p><b>CI:</b> confidence interval; <b>DFO:</b> deferoxamine; <b>DFX:</b> deferasirox; <b>MD:</b> mean difference; <b>RCT:</b> randomised controlled trial; <b>RR:</b> risk ratio; <b>SD:</b> standard deviation.</p> <p><b>GRADE Working Group grades of evidence</b>  <b>High certainty:</b> we are very confident that the true effect lies close to that of the estimate of the effect  <b>Moderate certainty:</b> we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different  <b>Low certainty:</b> our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect  <b>Very low certainty:</b> we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect</p>						

<sup>1</sup> We downgraded the quality of evidence by 2 due to high or uncertain risk of bias in several domains

<sup>2</sup> We downgraded the quality of evidence by 1 due to imprecision as CIs are wide and only 1 trial with data in comparison

DFX film-coated tablet compared to DFX dispersible tablet for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFX film-coated tablet <b>Comparison:</b> DFX dispersible tablet						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFX dispersible tablet	Risk with DFX film-coated tablet				
Adherence to iron chelation therapy (n, N)	Study population		RR 1.10 (95% CI 0.99 to 1.22)	173 (1 RCT)	⊕⊕○○ LOW <sup>1</sup>	
	849 per 1000	934 per 1000 (840 to 1000)				
Incidence of SAEs	Study population		RR 1.22 (95% CI 0.62 to 2.37)	173 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	
	151 per 1,000	184 per 1000 (94 to 358)				
All-cause mortality	Study population		RR 2.97 (95% CI 0.12 to 71.81)	173 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	
	0 per 1000	0 per 1000 (0 to 0)				
Sustained adherence - not measured	-	-	-	-	-	Reported as adherence as trial was 6 months in duration and end of trial adherence reported
Quality of life - not reported	-	-	-	-	-	



\***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **DFX:** deferasirox; **RCT:** randomised controlled trial; **RR:** risk ratio; **SAEs:** serious adverse events

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence by 2 for risk of bias due to high or unclear risk of bias in all domains

<sup>2</sup> We downgraded the quality of evidence by 1 for imprecision due to wide CIs

DFP and DFO compared to DFP for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFP and DFO <b>Comparison:</b> DFP						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFP	Risk with DFP and DFO				
Adherence to iron chelation therapy (per cent, SD)	see comment	see comment	-	289 (3 RCTs)	⊕○○○ VERY LOW <sup>12</sup>	Reported as narrative as no comparisons possible
Incidence of SAEs	Study population		RR 0.15 (95% CI 0.01 to 2.81)	213 (1 RCT)	⊕⊕○○ LOW <sup>23</sup>	
	28 per 1,000	4 per 1,000 (0 to 78)				
All-cause mortality	Study population		RR 0.77 (95% CI 0.18 to 3.35)	237 (2 RCTs)	⊕○○○ VERY LOW <sup>34</sup>	
	33 per 1,000	26 per 1,000 (6 to 112)				
Sustained adherence - not measured	-	-	-	-	-	Sustained adherence is reported as adherence as trial duration longer than 6 months and reports adherence for length of trial
Quality of life - not reported	-	-	-	-	-	Quality of life was either not reported or no validated instruments were used

\***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **DFO:** deferoxamine **DFP:** deferiprone; **RCT:** randomised controlled trial; **RR:** risk ratio; **SAEs:** serious adverse events; **SD:** standard deviation.

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence by 2 for risk of bias as there was high or uncertain risk of bias in most domains in 3 out of 4 trials

<sup>2</sup> We downgraded the quality of evidence by 1 due to high or unclear risk of bias in 3 domains

<sup>3</sup> We downgraded the quality of evidence by 1 for imprecision due to wide CIs

<sup>4</sup> We downgraded the quality of evidence by 2 for risk of bias as there was high or uncertain risk of bias in 1 of the trials in the comparison

DFP and DFO compared to DFO for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFP and DFO <b>Comparison:</b> DFO						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFO	Risk with DFP and DFO				
Adherence to iron chelation therapy (per cent, SD)	see comment	see comment	-	205 (4 RCTs)	⊕⊕○○ LOW <sup>1</sup>	Reported as narrative only as adherence in combined group not reported for combination therapy
Incidence of SAEs	Study population		-	205 (4 RCTs)	⊕⊕○○ LOW <sup>1</sup>	3 trials report no SAEs; SAES are not reported in one trial
	see comment	see comment				
All-cause mortality	Study population		-	205 (4 RCTs)	⊕⊕○○ LOW <sup>1</sup>	no deaths reported
	see comment	see comment				
Sustained adherence - not measured	-	-	-	-	-	Sustained adherence reported as adherence as trial duration was longer than 6 months and adherence reported at end of trial
Quality of life - not reported	-	-	-	-	-	

\***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**DFO:** deferoxamine; **DFP:** deferiprone; **SAEs:** serious adverse events.

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence by 2 for risk of bias as high or unclear risk of bias in all domains

DFP/DFO compared to DFP/DFX for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatients <b>Intervention:</b> DFP/DFO <b>Comparison:</b> DFP/DFX						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFP/DFX	Risk with DFP/DFO				
Adherence to iron chelation therapy rates (n,N) - 1 year	Study population		RR 0.84 (95% CI 0.72 to 0.99)	96 (1 RCT)	⊕⊕○○ LOW <sup>12</sup>	
	938 per 1000	788 per 1000 (675 to 928)				
Incidence of SAE	Study population		RR 1.00 (95% CI 0.06 to 15.53)	96 (1 RCT)	⊕○○○ VERY LOW <sup>123</sup>	
	21 per 1,000	21 per 1000 (1 to 324)				
All-cause mortality - at 1 year - trial end	Study population		Not estimable	96 (1 RCT)	⊕⊕○○ LOW <sup>12</sup>	No deaths were reported
	0 per 1000	0 per 1000 (0 to 0)				
Sustained adherence - not measured	-	-	-	-	-	Sustained adherence is reported as adherence as trial was 1 year in duration and end of trial adherence reported
Quality of life see comment	-	-	-	-	-	The study uses SF36 to measure quality of life, the results are presented as a graph. Qual-

			ity of life increased in both trial arms with no significant difference between trial arms P = 0.860
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\* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **DFO:** deferoxamine; **DGP:** deferiprone; **DFX:** deferasirox; **RCT:** randomised controlled trial; **RR:** risk ratio.

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence by 1 for risk of bias as there was high or unclear risk of bias in 3 domains

<sup>2</sup> We downgraded the quality of evidence by 1 for indirectness as the trial included children 10 - 18 with severe iron overload

<sup>3</sup> We downgraded the quality of evidence by 1 for imprecision as the comparison has wide CIs

Medication management compared to standard care for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia						
<b>Patient or population:</b> improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia <b>Setting:</b> outpatient <b>Intervention:</b> medication management <b>Comparison:</b> standard care						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with medication management				
Adherence to iron chelation therapy - not reported			-	-	-	Adherence was only reported in the intervention group and therefore no comparative data
SAEs - not reported	-	-	-	-	-	
Mortality - not reported	-	-	-	-	-	
Sustained adherence	-	-	-	-	-	Adherence was only reported in the intervention group and therefore no comparative data
Quality of life assessed with: Ped-sQLTM HRQoL total score			-	48 (1 RCT)	⊕○○○ VERY LOW <sup>12</sup>	Medication management: 63.51 (51.75 - 84.54); standard care: 49.84 (41.9 - 60.81)



\***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**RCT**: randomised controlled trial; **SAEs**: serious adverse events.

#### GRADE Working Group grades of evidence

**High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty**: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty**: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty**: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup> We downgraded the quality of evidence for indirectness by 2 because most outcomes were only reported in the medication management group

<sup>2</sup> We downgraded the quality of evidence by 2 for risk of bias due to high or uncertain risk of bias in all domains

## DISCUSSION

Regularly transfused people with SCD, as well as transfusion-dependent, and non-transfusion-dependent people with thalassaemia, are at risk of iron overload. Iron overload can lead to iron toxicity, with organs such as the heart, liver and endocrine glands being particularly vulnerable.

In this review we reviewed the evidence for improving adherence to iron chelation therapy in people with SCD or thalassaemia.

Sixteen RCTs with a total of 1525 participants met our inclusion criteria. Fourteen trials included people with  $\beta$ -thalassaemia major, one trial was conducted in people with SCD and another in people with  $\beta$ -thalassaemia intermedia, a milder form of  $\beta$ -thalassaemia. Trials were conducted between 1997 and 2017 and all included trials were medication interventions, except for one, which was a medication management intervention.

We also identified an additional five ongoing RCTs, and two studies awaiting classification (one RCT and one prospective cohort study).

We did not identify any cluster randomised trials, NRSIs, CBA or ITS studies that met the inclusion criteria.

### Summary of main results

The findings of the review led to the following main conclusions regarding medication interventions to improve adherence to iron chelation.

#### DFP versus DFO

Based on results from four trials in thalassaemia, we are uncertain whether oral DFP increases adherence to iron chelation therapy more than subcutaneous DFO (Calvaruso 2015; El Beshlawy 2008; Olivieri 1997; Pennell 2006). Results could not be combined due to a lack of data to report as well as the considerable heterogeneity between comparisons ( $I^2 = 99\%$ ). There was high adherence in all trials. We are uncertain if switching to oral DFP increases the risk of agranulocytosis compared to subcutaneous DFO. Oral DFP may have little or no effect on mortality compared to subcutaneous DFO. Quality of life was not measured in any trial in this comparison.

#### DFX versus DFO

Based on results from three trials, two in thalassaemia (Hassan 2016; Pennell 2014) and one in SCD (Vichinsky 2007), we are uncertain if DFX increases the rate of adherence compared to people taking DFO; participants had high adherence in all trials. We are uncertain whether DFX decreases risk of thalassaemia-related SAEs or decreases the risk of mortality in people with thalassaemia compared to DFO. We are uncertain whether DFX

decreases the risk of SCD-related pain crisis or other SCD-related SAEs compared to DFO. QoL was not reported in any trial in this comparison.

#### DFX (film-coated tablet (FCT)) versus DFX (dispersible tablet (DT))

Based on results from a single trial in thalassaemia, DFX FCT may make little or no difference to adherence as compared to DFX DT (Taher 2017). There was high adherence in both arms of the trial. We are uncertain if DFX FCT increases SAEs or all-cause mortality as compared to DFX DT. QoL was not measured using a validated instrument.

#### DFP and DFO combined versus DFP alone

Based on results from three trials in thalassaemia, we are uncertain if DFP and DFO combined increases adherence compared to DFP alone (Aydinok 2007; El Beshlawy 2008; Maggio 2009). There was high adherence in all trials. Combination therapy with DFP and DFO may make little or no difference to the incidence of SAEs as compared to DFP alone. We are uncertain if combination therapy with DFP and DFO decreases mortality as compared to DFP alone. QoL was not measured using a validated instrument.

#### DFP and DFO combined versus DFO alone

Based on results from four trials in people with thalassaemia, combined therapy with DFP and DFO versus DFO alone, may make little or no difference to adherence rates, SAEs, or mortality (El Beshlawy 2008; Galanello 2006; Mourad 2003; Tanner 2007). There was high adherence in all trials. QoL was not measured in any trial in this comparison.

#### DFP and DFO combined versus DFP and DFX combined

Based on the results of a single trial in children with thalassaemia, combination therapy with DFP and DFX may improve adherence to iron chelation therapy compared to combination therapy with DFP and DFO (Elalfy 2015). There was high adherence in both arms. We are uncertain if DFP and DFX reduces the incidence of SAEs, and may make little or no difference in mortality or QoL, compared to combination therapy with DFP and DFO.

#### Medication management versus standard care

A single trial on thalassaemia reported on this comparison (Bahnasawy 2017). Adherence rates were only reported in the intervention arm and therefore there are no comparative data to report. We are uncertain if medication management improves health-related QoL.

## Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of interventions to improve adherence to iron chelation therapy in people with SCD and thalassaemia. We have also identified five ongoing trials and two trials that are awaiting classification.

Of the five ongoing trials, two compare medication interventions in thalassaemia and two in SCD and thalassaemia ([EudraCT 2012-000353-31](#); [IRCT2015101218603N2](#); [NCT02173951](#); [NCT02435212](#)), and one assesses the effectiveness of group medical appointments on self-efficacy and adherence in SCD ([Madderom 2016](#)). Of the two studies awaiting classification, one is an educational study ([Antmen 2013](#)), and one is a medication intervention ([NCT00004982](#)).

The results of this review can only be interpreted in consideration of the following factors.

- Adherence is not the primary outcome in any of the included trials.
- All trials, except for one medication management trial, are medication interventions and participants were often selected based on their anticipated compliance. Lack of adherence was a reason for exclusion from some trials or analyses of results.
- Within the context of a clinical trial, there is increased attention by, and involvement of, clinicians and specialist nurses with participants which may impact and increase rates of adherence not seen in a community setting.
- Research has shown that up to 50% of people do not take medications as prescribed and over 85% of people are occasionally non-adherent to prescribed medications ([Ryan 2014](#)). The reported adherence rates in the trials included in this review are substantially higher than average, despite the substantial side effects and demanding administration regimen of iron chelators. This may be indicative of high adherence rates being an artefact created by participant involvement in a clinical trial.
- We did not identify any cluster randomised trials, NRSIs, CBA or ITS studies with adherence as a primary outcome, that met the inclusion criteria.
- Due to a lack of evidence this review cannot comment on intervention strategies for different age groups.

## Quality of the evidence

Overall the quality of the evidence according to GRADE methodology across all comparisons for the outcomes of adherence, SAEs, and mortality was rated as low to very low ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#); [Summary of findings 6](#); [Summary of findings 7](#)). This was due to trials being at serious or very serious risk of bias; outcome estimates being imprecise (wide CIs); and indirectness with some

trials conducted only in children of a specific age and meeting specific criteria. QoL was mostly not reported or reported using non-validated measurements or sparsely reported with no data.

## Potential biases in the review process

To our knowledge, our review process was free from bias. We conducted a comprehensive search: searching data sources (including multiple databases, and clinical trial registries) to ensure that all relevant studies would be captured. There were no restrictions for the language in which the paper was originally published. The relevance of each paper was carefully assessed and all screening and data extractions were performed in duplicate. We pre-specified all outcomes and subgroups prior to analysis. There were insufficient numbers of included trials within the meta-analyses for us to use a funnel plot to examine the risk of publication bias.

## Agreements and disagreements with other studies or reviews

Adherence rates can vary widely, a recent review reported that adherence rates to the oral iron chelator DFX ranged between 22% and 89% ([Loiselle 2016](#)). Another review of medication adherence in SCD reports adherence rates ranging from 16% to 89%; but most included studies reported moderate adherences ([Walsh 2014](#)). In this Cochrane Review, we found adherence rates across trials and for all comparisons of different chelators to be quite high in individual trial reports (predominantly at least 80%). Indeed the results of this review are in disagreement with most literature that identifies major issues with compliance across indications, people and setting ([NICE 2009](#); [Ryan 2014](#); [WHO 2003](#)). We suggest that selection bias for compliance into the chelation trials as a possible reason for high adherence; as well, the additional time and attention received by participants make high adherence an artefact of trial participation.

Ryan identifies several strategies that may help to promote adherence including self-management; self-monitoring; simplified dosing regimens; or interventions involving pharmacists in medication management ([Ryan 2014](#)). Other identified interventions that need further research include pragmatic interventions (such as reminders); educational interventions, and financial incentives. One RCT on pharmacist-led medication management was included in this review, but the trial had few participants, was of short duration and poorly reported ([Bahnasawy 2017](#)). The remaining trials in this review measured compliance primarily as a secondary outcome and did not identify any specific strategies that may have led to increased compliance, thus supporting the contention that high compliance is an artefact of participation in these trials and not the result of change or improvement in medication regimens.

## AUTHORS' CONCLUSIONS

### Implications for practice

Adherence to iron chelation regimens can reduce morbidity and mortality in people with transfusion- and non-transfusion-dependent thalassaemia and sickle cell disease. Iron chelation regimens can be demanding and also have unpleasant side effects that reduce adherence to these medications. In this review we did not identify any specific medication intervention that increased adherence with iron chelators and suggest that adherence was high due to the artefact of participation in these trials. Due to a lack of evidence, this review cannot comment on intervention strategies for different age groups.

Overviews of systematic reviews that identify intervention strategies that have been successful for other indications and medications may be more useful to clinicians who want to improve compliance with iron chelation therapy. However, the successful translation of these interventions to iron chelation regimens would still need to be confirmed in appropriate trials.

### Implications for research

Real-world, pragmatic trials in community and clinic settings are needed to examine a variety of confirmed or unconfirmed adherence strategies that may be useful to increase adherence to iron

chelation therapy. High-quality, non-randomised trials that measure compliance over multiple time points, before and after an intervention, as well as non-randomised studies that test interventions in multiple settings could help to identify evidence-based strategies that increase compliance with iron chelation therapy. Finally, appropriate measurements of compliance are needed that include both patient-oriented, such as quality of life measurements, as well as objective measurements that link iron levels and morbidity due to iron overload to levels of adherence. Targeted strategies that increase adherence in different age groups, particularly in adolescents, are also needed.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Aydinok 2007

Methods	<b>Study design:</b> single-centre RCT <b>Study grouping:</b> parallel group <b>Study duration:</b> treatment duration 12 months; follow-up: not stated
Participants	<b>Baseline characteristics</b> <b>DFP, DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: 12 randomised; 8 analysed</li> <li>• Age mean (SD): 16.6 (4.8) years, range 9 to 23 years</li> <li>• Sex: not reported</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): 100% <math>\beta</math>-thalassaemia</li> <li>• Baseline ferritin levels (ng/mL) mean (SD): 4453 (2858)</li> <li>• Previous iron chelation: not reported</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g) mean (SD): 27.0 (13.4)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Hb, g/L mean (SD): 89 (5)</li> </ul> <b>DFP</b> <ul style="list-style-type: none"> <li>• Total # of participants: 12</li> <li>• Age mean (SD): 15.9 (4.2) years</li> <li>• Sex: not reported</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): 100% <math>\beta</math>-thalassaemia</li> <li>• Baseline ferritin levels (ng/mL): 4070 (3223)</li> <li>• Previous iron chelation: not reported</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g): 30.7 (10.6)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Hb, g/L mean (SD): 89 (5), range 9 to 23 years</li> </ul> <b>Inclusion criteria:</b> iron-overloaded people with thalassaemia at least 4 years old <b>Exclusion criteria:</b> lack of compliance, known toxicity or intolerance preventing therapy with DFO and DFP, neutropenia (neutrophils $< 1.5 \times 10^9/L$ ), thrombocytopenia (platelets $< 100 \times 10^9/L$ ), renal, hepatic or decompensated heart failure, active viral illness being treated with interferon- $\alpha$ /ribavirin, repeated Yersinia infections, HIV-positivity, pregnancy or nursing, and patients of reproductive age not taking adequate contraceptive precautions
Interventions	<b>Treatment arm:</b> DFO (50 mg/kg/day subcutaneously twice weekly (mean (SD) dose: 43.8 (2.8) mg/kg)) combined with DFP (75 mg/kg/day, daily (mean (SD) dose: 78.2 (1.4) mg/kg/day)) <b>Comparator arm:</b> DFP (75 mg/kg/day, daily (mean (SD) dose: 78.2 (2.6) mg/kg/day))

Outcomes	<b>Adherence:</b> compliance was assessed by drug accounting at each visit (by counting the returned empty blisters of DFP and used vials of DFO) as well as by a trial-specific questionnaire completed by the participants and/or their legal representative/guardian at quarterly intervals The same questionnaire also served for the assessment of tolerance to treatment and QoL <b>Trial-reported outcomes</b> 1. Changes in LIC and SF (primary outcome) 2. Total iron excretion 3. Urinary iron excretion 4. Iron balance 5. Cardiac function (Echo) 6. Toxicity 7. Assessment of tolerance to treatment and QoL	
Identification	Source of funding: none stated although the drugs were supplied by Lipomed AG, Switzerland	
Notes	All participants had prior exposure to DFO (dose, schedule and duration were not reported) and all had a washout period of 2 weeks with no iron chelation before initiating trial treatment Sample-size calculation not reported <b>Country:</b> Turkey	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	“The randomization sequence was generated by the Department of Mathematical Statistics at the University of Berne, Switzerland according to local policy”. Following central registration of a subject by the investigator, the trial co-ordinator assigned the intervention according to the randomisation sequence
Allocation concealment (selection bias)	High risk	The trial report states that the intervention was assigned according to the randomisation sequence “without concealing the sequence prior to allocation”
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	The authors did not report any information as to whether participants, personnel were blinded to treatment allocation but one treatment subcutaneous and other oral so difficult to blind

Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	There was an imbalance in missing data across the treatment arms. 4 participants from the comparator group (DFO) were not included in the outcome analysis: 2 withdrew consent due to refusal to take DFO; 1 died from arrhythmia induced congestive heart failure at start of trial; and 1 developed agranulocytosis at week 14
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	There is an imbalance in baseline LIC and Ferritin between groups

# Badawy 2010

Methods	<b>Study design:</b> RCT <b>Study grouping:</b> parallel group Length of trial or follow-up not stated. Not stated if open label; but no mention of blinding and DFO is infusion versus tablet
Participants	<b>Baseline characteristics</b> <b>DFO, DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: 50</li> <li>• Age: <math>\geq 8</math> years</li> <li>• Sex: not reported</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): 100% <math>\beta</math>-thalassaemia</li> <li>• Baseline ferritin levels (ng/mL): not reported</li> <li>• Previous iron chelation: DFO</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g): not reported</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <b>DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: 50</li> <li>• Age: <math>\geq 8</math> years</li> <li>• Sex: not reported</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): <math>\beta</math>-thalassaemia</li> <li>• Baseline ferritin levels (ng/mL): not reported</li> <li>• Previous iron chelation: DFO</li> </ul>

	<ul style="list-style-type: none"> <li>• Duration of any iron chelation: not reported</li> <li>• Liver iron concentration LIC (mg/g): not reported</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 50</li> <li>• Age: greater or equal to 8 years</li> <li>• Thalassaemia genotype N (%): 100% <math>\beta</math>-thalassaemia</li> <li>• Baseline ferritin levels (ng/mL): not reported</li> <li>• Previous iron chelation: DFO</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g): not reported</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>Inclusion criteria:</b> 8 years, RBC transfusion every 3 to 4 weeks, on DFO prior to study as single therapy</p> <p><b>Exclusion criteria:</b> not stated</p> <p>Participants PRBCs /3 - 4 weeks to maintain Hb &gt; 9 g/dL</p>
Interventions	<p><b>DFP, DFO</b></p> <ul style="list-style-type: none"> <li>• Medication intervention: daily DFP, DFO twice-weekly DFO (40 mg/kg/day); Deferipron e (75 mg/kg/day).</li> </ul> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• Medication intervention: daily DFP Deferipron e (75 mg/kg/day).</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Medication intervention: DFO 5 days/week DFO (40 mg/kg/day)</li> </ul>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates</p> <p>Questionnaire on chelation therapy, reasons for non-compliance, side effects, life activities, transfusion regimen</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. CBC monthly</li> <li>2. SF levels</li> <li>3. liver and kidney functions</li> <li>4. blood glucose level</li> <li>5. serum calcium and phosphorus/3 months and T3, T4,TSH, LH, FSH</li> <li>6. echocardiography</li> <li>7. bone density</li> <li>8. auditory and visual examination twice</li> </ol>
Identification	<p><b>Sponsorship source:</b> Zagazig University Hospital, Zagazig</p> <p><b>Country:</b> Egypt</p> <p><b>Setting:</b> University Hospital</p> <p><b>Comments:</b> Abstract Poster 124</p> <p><b>Authors name:</b> Sherif Badawy</p> <p><b>Institution:</b> Ann Robert H. Lurie Children's Hospital of Chicago</p> <p><b>Email:</b> sbadawy@luriechildrens.org</p>

**Badawy 2010** (Continued)

	<b>Address:</b> Ann Robert H. Lurie Children’s Hospital of Chicago Northwestern University Feinberg School of Medicine225 East Chicago Avenue, Box 30, Chicago, Illinois 60611-2605	
Notes	Contacted author and study data not available at this time. Sample-size calculation not reported	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Judgement comment: no description of sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment no description, but one drug is subcutaneous injection (DFO) . Open label
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	Judgement comment: no description of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: no data on number of participants who completed the study and how many in each group experienced complications. Lack of detail on number of compliant or non-compliant participants
Selective reporting (reporting bias)	High risk	Judgement comment: not clear which groups and how many experienced adverse events. No data reported on SF or other outcomes
Other bias	Unclear risk	Judgement comment: results of the trial were not published in detail and no data available when authors were contacted

**Bahnasawy 2017**

Methods	<b>Study design:</b> single-centre RCT <b>Study grouping:</b> parallel group <b>Study duration:</b> 6 months
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Participants	<p><b>Baseline characteristics</b></p> <p>Comprehensive medication management</p> <ul style="list-style-type: none"> <li>• Total # of participants: 24</li> <li>• Age (mean (SD)): 12 (2.7)</li> <li>• Sex N (%): F: 15 (62.5); M: 9 (37.5)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype (%): <math>\beta</math>-thalassaemia major 100%</li> <li>• Baseline ferritin levels (ng/mL) (mean (SD)): 3949 (1864)</li> <li>• Previous iron chelation: N/A</li> <li>• Duration of any iron chelation: N/A</li> <li>• LIC (mg/g): not stated</li> <li>• Splenectomy n (%): 6 (25.9)</li> <li>• QoL PedsQL median (IQR): 55.16 (43.42 - 63.75)</li> <li>• Hb, g/L: not stated</li> </ul> <p>Standard care (as defined in the trial)</p> <ul style="list-style-type: none"> <li>• Total # of participants: 24</li> <li>• Age (mean (SD)): 13 (2.8)</li> <li>• Sex N (%): F: 15 (62.5); M: 9 (37.5)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype (%): <math>\beta</math>-thalassaemia major 100%</li> <li>• Baseline ferritin levels (ng/mL) (mean (SD)): 3871 (1881)</li> <li>• Previous iron chelation: N/A</li> <li>• Duration of any iron chelation: N/A</li> <li>• LIC (mg/g): not stated</li> <li>• Splenectomy n (%): 9 (37.5)</li> <li>• QoL PedsQL median (IQR): 49.12(38.13 - 56.95)</li> <li>• Hb, g/L: not stated</li> </ul> <p><b>Inclusion criteria:</b> transfusion-dependent children with <math>\beta</math>-thalassaemia major aged 8 to 18 years with SF level of more than 1000 <math>\mu</math>g/L</p> <p><b>Exclusion criteria:</b> people with cognitive impairment</p>
Interventions	<p><b>Comprehensive medication management</b></p> <ul style="list-style-type: none"> <li>• interview with participants at each visit, drug-related problems identified, care plan introduced / monitored to include dosage modification, education. Follow-up compliance via regular phone calls</li> </ul> <p><b>Standard care (as defined in the trial)</b></p> <ul style="list-style-type: none"> <li>• all participants presented to the clinic regularly every 2 - 4 weeks according to the need for receiving blood transfusion, blood samples were drawn for CBC assessment. Physical examination was done by physician including assessment of hepatomegaly, splenomegaly and any health-related problems</li> </ul>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates</p> <p>“DRP identification: The clinical pharmacist analysed the collected data to detect whether any DRPs existed and allocated them to one of the seven categories as classified by Cipolle et al. [18]: unnecessary drug therapy, need for additional drug therapy, ineffective drug product, dosage too low, adverse drug reaction, dosage too high, non-compliance”</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. SF levels were measured at baseline, 3 months and after 6 months</li> </ol>

	2. CBC with WBC differential was assessed at every visit, and SCr and ALT were measured routinely for all the participants every 3 months 3. Health-related QoL was assessed at baseline and at the end of the trial (after 6 months) using PedsQL™ 4.0 Generic Core Scale questionnaire. PedsQL is a 23-item multidimensional model with 4 domains for paediatric health-related QoL measurement: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items) (19)	
Identification	<b>Sponsorship source:</b> not stated <b>Country:</b> Egypt <b>Setting:</b> Hematology clinic <b>Authors name:</b> Lamia El Wakeel <b>Institution:</b> Pediatric Hematology Clinic, Children’s Hospital, Ain Shams University, <b>Email:</b> lamywak@yahoo.com <b>Address:</b> Lamia El Wakeel, Pediatric Hematology Clinic, Children’s Hospital, AinShams University, 4, Street 292 New Maadi, Cairo, Egypt	
Notes	Sample-size calculation not reported. Drug-related outcomes do not have any comparable data reported. Only outcomes with comparable data reported are SF levels and health-related QoL	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote: “The study was a prospective, randomized, controlled study. It was conducted on pediatric BTM patients admitted to the Pediatric Hematology Clinic,” Stratified randomization was used considering the iron chelation therapy as the stratification factor Judgement comment: no description of how randomisation was done or by whom
Allocation concealment (selection bias)	Unclear risk	The control group (n = 24) received standard medical care by a physician while the intervention group received standard medical care plus clinical pharmacist-provided services Judgement comment: no description of how participants were allocated to the pharmacist intervention or standard care
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: not possible to blind a pharmacist intervention versus no pharmacist intervention

Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Judgement comment: no indication that outcome assessors were different from pharmacists who implemented the intervention. Also most outcomes were reported only in the intervention group except for ferritin levels and health-related QoL
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: all drug-related outcomes were only reported in the intervention group including adherence - no comparative data available. Multiple interventions in small number of participants
Selective reporting (reporting bias)	High risk	Judgement comment: drug-related outcomes reported only in intervention group. No comparative data. The participants within the intervention arm seem to have complex and multiple changes. Difficult to tease out the actual intervention that effected a change
Other bias	Unclear risk	Judgement comment: small sample size and only report intervention group

## Calvaruso 2015

Methods	<p><b>Study design:</b> RCT</p> <p><b>Study grouping:</b> parallel group</p> <p>This trial was designed as a 5-year, multicentre, randomised, open-label trial with blinded data management and data analyses to evaluate whether the DFP treatment is superior to the DFO treatment</p> <p>Follow-up after trial. An additional 5 years of follow-up after the end of the trial was planned to collect data on the survival, cause of death and chelation treatment of this cohort of participants. During this period, the participants were allowed to change their chelation treatment</p>
Participants	<p><b>Baseline characteristics</b></p> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 47</li> <li>• Age: mean (SD): 41.3 (14.8)</li> <li>• Sex n (%): F: 24 (50)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype (%): thalassaemia Intermedia 100%</li> <li>• Baseline ferritin levels (ng/mL) median (IQR): 1221 (743)</li> <li>• Age at initiation of DFO years: mean (SD): 29.9 (16.8)</li> <li>• LIC (mg/g/dw) median (IQR): 3800 (2800)</li> <li>• Splenectomy n (%): 42 (89.3)</li> <li>• QoL: mean (SD): not reported</li> </ul>

	<ul style="list-style-type: none"> <li>• Hb, g/L mean (SD): 88 (10)</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 41</li> <li>• Age: mean (SD): 41.2 (14.3)</li> <li>• Sex n (%): F: 23 (51.1)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype (%): thalassemia intermedia 100%</li> <li>• Baseline ferritin levels (ng/mL) (median (IQR)): 1,122 (910)</li> <li>• Age at initiation of DFO years: mean (SD): 29.6 (17.4)</li> <li>• LIC (mg/g/dw) median (IQR): 3800 (4668)</li> <li>• Splenectomy n (%): 35 (77.7)</li> <li>• QoL: mean (SD): not reported</li> <li>• Hb, g/L mean (SD): 89 (12)</li> </ul> <p><b>Inclusion criteria:</b> people with thalassaemia intermedia (based on clinical and molecular criteria), SF between 800 and 3000 µg/L, 13 years of age, consent from patient or parent or guardian (if 13 to 18)</p> <p><b>Exclusion criteria:</b> known intolerance to treatment, platelet count &lt; 100 × 10<sup>9</sup>/L, white cell count of &lt; 3 × 10<sup>9</sup>/L, severe liver damage, sepsis or heart failure (or both)</p> <p><b>Pretreatment:</b> none of the participants in the DFP group and 8 in the DFO group withdrew from the trial. 1 participant in the DFP group and 3 in the DFO group changed their chelation therapy (P value = 0.357)</p> <p>If the participants were treated with a subcutaneous administration of DFO (30 - 50 mg/kg per day, 8 - 12 hours for 5 days a week) before inclusion in the trial, a DFO washout was executed for 1 week before randomisation. The minimum number of participants required for each treatment group was calculated, assuming equal allocation under the hypothesis of equality between the 2 treatment groups at each point during the course. The recommended number of participants was 30</p> <p>One participant in the DFP group and 3 in the DFO group changed their chelation therapy</p>
Interventions	<p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• DFP (Apotex; Toronto, ON, Canada) administered at 75 mg/kg/day, divided into 3 oral daily doses for 7 days/week</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• DFO (BiofuturaPharma, Omezia, Italy), administered by subcutaneous infusion (8 - 10 hours) at 50 mg/kg per day for 5 days/week</li> </ul> <p>Treatment failure was defined as an increase in the SF level to greater than 1000 lg/L from baseline, confirmed by at least 2 consecutive determinations. Participants who failed were switched to the alternative treatment and followed until the end of the trial. The criteria for a dosage reduction to 50 mg/kg of DFP per day were arthralgia and nausea, and the criterion for a reduction to 30 mg/kg of DFO per day was a local reaction at the site of infusion. Both treatments were reduced if the ferritin levels for 2 consecutive determinations were less than 400 lg/L. The treatment was resumed when the ferritin levels were greater than 700 lg/L for at least 2 determinations</p>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates</p> <p><b>Compliance</b> was assessed by counting the number of DFP pills in each returned bag and by assessing the number of infusions of DFO registered on the electronic pump</p> <p><b>Trial-reported outcomes</b></p>

	1. The primary endpoint was treatment effectiveness, evaluated as the mean change in the SF level over the 5-year period. This type of evaluation strengthened the power of the test for the sample-size calculation compared with the standard 2. The secondary endpoints were safety and survival analysis after 5 years	
Identification	<b>Sponsorship source:</b> contract grant sponsor: Franco and Piera Cutino Foundation <b>Country:</b> Italy (17 centres) <b>Setting:</b> haematology and thalassaemia clinical centres at institutions <b>Recruitment:</b> January 2001 to January 2006 <b>Trial registration:</b> NCT00733811 <b>Authors name:</b> Aurelio Maggio <b>Institution:</b> Unita Operativa Complessa Ematologia II, <b>Email:</b> md.amaggio@gmail.com <b>Address:</b> U.O.C. Ematologia II, A.O.R. “Villa Sofia - V. Cervello”, Palermo, Italy	
Notes	Sample-size calculation reported for primary outcome <b>Notes:</b> 9 participants changed from DFP therapy 5 to DFO 2 to none 1 to DFX 1 to DFP-DFO 6 participants changed from DFO therapy 4 to DFP 1 to DFX 1 to DFP-DFO	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote: “The randomization sequence was based on a computer- randomized list arranged in permuted blocks of 10 with a 1: 1 ratio.”
Allocation concealment (selection bias)	Low risk	To ensure for allocation concealment, treatments were assigned by telephone contact from the coordinating centre. The sequence was concealed until the interventions were assigned. Randomization was performed for each consecutive patient after verification of the exclusion criteria
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Quote: “open-label trial” Judgement comment: 1 of 2 arms was desferal pump infusers, participants would know. Participants on DFO attended for weekly blood tests

**Calvaruso 2015** (Continued)

Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: “with blinded data management and data analysis”
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up for 5-year trial
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Unclear how participant variation relating to SF levels may have had effect on results. Although all outcomes were reported for the 5 year trial in the 5 years of follow-up only mortality was reported

**El Beshlawy 2008**

Methods	<b>Study design:</b> single-centre RCT <b>Study grouping:</b> parallel group, follow-up for 54 weeks
Participants	<b>Baseline characteristics</b> <b>DFP/DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: 18</li> <li>• Age (mean (SD): 11.0 (4.9)</li> <li>• Sex: F: 10; M: 8</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%) : <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ug/mL) (mean (SD) (range)): 2865 (983) (1500 - 4800)</li> <li>• Previous iron chelation: not reported</li> <li>• LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 - 33.6) N = 16</li> <li>• Splenectomy n (%): 11 (61)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L (mean (SD) (range): 68 (5) (55 - 75)</li> </ul> <b>DFP</b> <ul style="list-style-type: none"> <li>• Total # of participants: N = 18</li> <li>• Age (mean (SD) (range)): 10.8 (5.1) (5 - 26)</li> <li>• Sex: F: 6; M: 12</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%) : <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ug/mL) (mean (SD) (range)): 2926 (1107) (1560 - 5000)</li> <li>• Previous iron chelation: not reported</li> <li>• LIC (mg/g) (mean (SD) (range)): 15.8 (7.1) (2.3 - 29.3) N = 17</li> <li>• Splenectomy n (%): 9 (50)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L mean (SD) (range): 69 (6) (58 - 80)</li> </ul> <b>DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: N = 20</li> </ul>

	<ul style="list-style-type: none"> <li>• Age (mean (SD) (range)): 13.1 (5.9) (5.5 - 24)</li> <li>• Sex: F: 9; M: 11</li> <li>• Ethnicity: not reported</li> <li>• Sick cell genotype N (%) - not applicable:</li> <li>• Thalassaemia genotype N (%): <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ug/mL) (mean (SD)(range)): 2 838 (967) (1500 - 4300)</li> <li>• Previous iron chelation: not reported</li> <li>• LIC (mg/g) mean (SD) (range): 22.5 (10.1) (6.0 - 41.7) N = 15</li> <li>• Splenectomy n (%): 10 (50)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L mean (SD) (range): 69 (5) (60 - 80)</li> </ul> <p><b>Inclusion criteria:</b> males or females with thalassaemia major attending the Hematology Clinic at Cairo University Children Hospital; participants had to be iron overloaded with transfusion dependency and older than 4 years of age</p> <p><b>Exclusion criteria:</b> known to have DFP or DFO toxicity; neutrophil count less than <math>1.5 \times 10^9/L</math>; platelet count less than <math>100 \times 10^9/L</math>; renal or hepatic insufficiency; decompensated heart failure; without contraceptive precaution; pregnant or nursing</p>
Interventions	<p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• DFP + DFO (dose 60 - 83 mg/kg/day and DFO 23 to 50 mg/kg per dose) DFP 7 days and DFO over 8 hours 2 days/week)</li> </ul> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• DFP only (dose 60 to 83 mg/kg/day) 7 days per week</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• DFO 23 to 50 mg kg/day monotherapy for 5 days/week</li> </ul>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates</p> <p>Compliance was assessed by performing a drug accounting at each patient visit by counting the returned empty blisters of DFP and used vials of DFO</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. Incidence of chelation therapy-related SAEs (reported in AEs)</li> <li>2. Iron overload defined by ferritin over 1000 <math>\mu g/L</math> and/or clinical symptoms and/or signs of iron overload and/or need for medically indicated additional or change in chelation therapy (mean ferritin levels extrapolated from graph - no SD provided)</li> <li>3. Other AEs related to iron chelation (in this trial participants with an event are reported. 1 person could experience more than 1 event)</li> <li>4. LIC mg/g dry weight (change from baseline (extrapolated from graph Least squares means / lower and upper value))</li> </ol>
Identification	<p><b>Sponsorship source</b></p> <p><b>Country:</b> Egypt</p> <p><b>Setting:</b> Hematology Clinic at Cairo University Children Hospital, Egypt</p> <p><b>Comments:</b> 2 authors from Lipomed (DFP): C. Manz : C. Tarabishi Clinical Research Development, Lipomed AG, Arlesheim, Switzerland</p> <p><b>Authors name:</b> A. El-Beshlawy</p> <p><b>Institution:</b> Faculty of Medicine, Cairo University,</p> <p><b>Email:</b> amalelbeshlawy@yahoo.com</p> <p><b>Address:</b> Faculty of Medicine, Cairo University, 32 Falaky Street, Bab El-Louk, Cairo, Egypt</p>

Notes	Sample-size calculation reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: no description of how randomisation was accomplished: The participants were randomly assigned into 1 of 3 treatment arms
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	No mention of blinding - since DFO is an injection and DFP is oral likely participants and personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	Judgement comment: no blinding mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: a total of 10 participants dropped out of the trial as a result of several complications. Only 56 participants completed 54 weeks of treatment. Evaluation of LIC could not be done in another 8 participants. Reports on per protocol participants
Selective reporting (reporting bias)	High risk	Compliance not reported as number or percentage of participants compliant throughout trial: "Four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study. The majority of patients had no problems with the intake and swallowing of the DFP tablets. By contrast, 80% of patients in the combination arm and 76% of patients in the DFO monotherapy arm complained about difficulties in the parenteral use of DFO or problems to insert a needle", SF and LIC are partially reported in charts and no actual numbers are provided in the text. Also the focus on UIE over LIC and SF measures is misleading as DFP



		is known to have a higher UIE but this can be highly variable over multiple measurements. LIC is the gold standard and there was no difference in this outcome between groups
Other bias	Unclear risk	There was a higher incidence of AEs in the combined group and the DFP group versus the DFO group

## Elalfy 2015

Methods	<b>Study design:</b> RCT in 2 treatment centres <b>Study grouping:</b> parallel group Study duration: 1 year
Participants	<b>Baseline characteristics</b> <b>Group A: DFP/DFO</b> <ul style="list-style-type: none"> <li>• Total # of participants: 48</li> <li>• Age: mean (SD): 15.25 (2.31)</li> <li>• Sex: male n (%): 30 (62.5)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): Not stated all participants appear to have <math>\beta</math>-thalassaemia major</li> <li>• Baseline ferritin levels (ng/mL): mean (SD): 4379.07 (895.00); range 3632 - 6210</li> <li>• Duration of any iron chelation (years): mean (SD): 8.71 (2.7)</li> <li>• LIC (mg/g): mean (SD): 12.69 (2.23); range: 12.69 - 2.23</li> <li>• Splenectomy n (%): 21 (43.7)</li> <li>• QoL mean (SD): 63.09 (5.77)</li> <li>• Hb, g/L mean (SD): 81.1 ( 3.3)</li> <li>• Mean geometric cardiac T2*(ms): mean (SD): 16.32 (1.82); range: 14.9 - 18.2</li> </ul> <b>Group B: DFP/DFX</b> <ul style="list-style-type: none"> <li>• Total # of participants: 48</li> <li>• Age: mean (SD): 14.05 (2.21)</li> <li>• Sex: male n (%): 32 (66.6)</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%): not stated all participants appear to have <math>\beta</math>-thalassaemia major</li> <li>• Baseline ferritin levels (ng/mL) mean (SD): 4289.19 (866.21); range: 3451 - 7122</li> <li>• Duration of any iron chelation (years): mean (SD): 8.95 (2.8)</li> <li>• LIC (mg/g): mean (SD): 12.52 (2.28); range: 9.82 - 15.12</li> <li>• Splenectomy n (%): 20 (41.6)</li> <li>• QoL mean (SD): 63.38 (5.98)</li> <li>• Hb, g/L mean (SD): 79 (3.8)</li> <li>• Mean geometric cardiac T2*(ms): mean (SD): 16.59 (1.85); range: 15.7 - 18.9</li> </ul> <b>Inclusion criteria:</b> people with $\beta$ -thalassaemia major aged 10 - 18 years with severe iron overload defined as: ferritin > 2500 $\mu$ g/L on maximum tolerated dose of a single iron chelator with up trend of ferritin over the last 12 months prior to the study. People

	<p>with LIC more than 7 mg/g by MRI R2* and mean cardiac T2* less than 20 and more than 6 ms calculated as geometric mean without clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnoea, exercise intolerance, lower extremity oedema, arrhythmias). Adequacy of prior chelation defined as taking 75% of the calculated dose/month on maximum tolerated dose with upward ferritin trend</p> <p><b>Exclusion criteria:</b> past history of agranulocytosis, clinically significant GI or renal disease, clinical cardiac disease, or with LVEF &lt; 50% on baseline echocardiography; evidence of active hepatitis or serum transaminases &gt; 3 times above ULN or renal impairment (serum creatinine &gt; ULN) participation in a previous investigational drug study within the 30 days preceding screening, known allergy to DFX, DFP, and DFO</p> <p><b>Pre-treatment:</b> baseline difference in mean Hb (P 0.004)</p>
Interventions	<p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• DFP 75 mg/kg/day divided into 2 doses taken orally at 8 a.m. and 3 p.m. for 7 days (with 6 - 8 hours interval between the 2 doses) combined with DFO 40 mg/kg/day by subcutaneous infusion over 10 hours starting at 10 p.m. for 6 days/week</li> </ul> <p><b>DFP/DFX</b></p> <ul style="list-style-type: none"> <li>• DFP 75 mg/kg/day, divided into 2 doses taken orally at 8 a.m. and 3 p.m. combined with DFX30 mg/kg/day taken orally at 10 p.m. for 7 days/week</li> </ul> <p>To achieve an acceptable treatment washout, chelation therapy was withdrawn for 2 weeks before randomisation, after verifying inclusion and exclusion criteria. The transfusion regimen aimed to maintain the participants pre-transfusion Hb <math>\geq</math> 80 g/L by receiving approximately 15 mL/kg packed RBCs every 3 - 4 weeks</p>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates</p> <p>Compliance was evaluated by counting of returned tablets for the oral chelators and of the vials for DFO. The percentage of actual dose that participant had taken in relation to the total prescribed dose was calculated</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. % change in SF (from baseline to the end of trial)</li> <li>2. % change in LIC (from baseline to the end of trial)</li> <li>3. % change in cardiac MRI (from baseline to the end of trial)</li> <li>4. SAEs and AEs (safety assessment)</li> <li>5. Compliance</li> <li>6. Satisfaction</li> <li>7. QoL</li> </ol>
Identification	<p><b>Sponsorship source:</b> Ain Shams University</p> <p><b>Country:</b> Egypt and Oman</p> <p><b>Setting:</b> Thalassemia treatment centres (Ain Shams University, Egypt and Sultan Qaboos University Hospital, Oman)</p> <p><b>Comments:</b> Government Clinical Trial NCT01511848</p> <p><b>Authors name:</b> Amira Abdel Moneam Adly,</p> <p><b>Institution:</b> Department of Pediatrics, Ain Shams University, Cairo, Egypt</p> <p><b>Email:</b> amiradiabetes@yahoo.com</p> <p><b>Address:</b> 6 A ElSheshini street, Shoubra, Soudia buildings, Cairo, Egypt</p>

Notes	The chelation regimens in the last year prior to the trial were daily DFX (14 participants) , daily DFP (29 participants), and DFP 4 days/week alternating with subcutaneous DFO 3 days/week (53 participants) Sample-size calculation reported Author contacted for additional info on SF 36 mean (SD) 6 months and end of trial	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The randomisation sequence was based on a computer randomised list in permuted blocks of 10 with a 1 : 1 ratio, generated at both University of Ain Shams and Sultan Qaboos”
Allocation concealment (selection bias)	Low risk	Quote: “To ensure no allocation bias, treatment group was assigned by telephone contact from the coordinating center in Ain Shams”
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Oral versus subcutaneous medication therefore participants would be aware which medication arm they had been randomised to
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: “open-label study with blinded data management and data analyses”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: treatment was started within the following 24 hr, and all the included participants continued till the end of study with no participants were lost follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: provide only P values for patient satisfaction, satisfaction with ICT self-reported satisfaction and all 'significantly' higher in group B; no actual end of trial data provided (mean (SD)). All outcomes are reported
Other bias	Unclear risk	Judgement comment: it is not clear how the investigators would have known that infections, GI disorders or skin disorders were not related to the drug therapies

Methods	<p><b>Study Design:</b> 2-arm parallel RCT conducted in Italy and Greece</p> <p><b>Number of centres:</b> multicentre (3 centres)</p> <p><b>Duration of treatment:</b> 12 month</p> <p><b>Follow-up:</b> not stated.</p>
Participants	<p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: randomised 30, analysed 29 (withdrawn after 2 days on trial before taking DFP)</li> <li>• Age (mean (SD)): 19.8 (6.1) years</li> <li>• Sex: F: 13; M: 16</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%) : <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ug/mL) mean (SD): 2048 (685)</li> <li>• Previous iron chelation: not reported</li> <li>• LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 - 33.6) N = 16</li> <li>• Splenectomy n (%): 11 (61)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L mean (SD) (range): 68 (5) (55 - 75)</li> </ul> <p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: randomised 30, analysed 30</li> <li>• Age (mean (SD)): 18.7 (4.8) years</li> <li>• Sex: F: 18; M: 12</li> <li>• Ethnicity: not reported</li> <li>• Thalassaemia genotype N (%) : <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ug/mL) (mean (SD): 2257 (748)</li> <li>• Previous iron chelation: not reported</li> <li>• LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 - 33.6) N = 16</li> <li>• Splenectomy n (%): 11 (61)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L mean (SD) (range): 68 (5) (55 - 75)</li> </ul> <p><b>Inclusion criteria:</b> participants were 10 years or older with a diagnosis of thalassaemia major undergoing iron chelation therapy with subcutaneous DFO, with a SF value between 1000 - 4000 <math>\mu</math>g/L over the previous year</p> <p><b>Exclusion criteria:</b> not reported</p>
Interventions	<p><b>DFO:</b> 20 - 60 mg/kg/day subcutaneously on 5 - 7 days a week (mean (SD) dose at baseline: 34.8 (8.9) mg/kg/day and at end of trial: 37.8 (8.9) mg/kg/day))</p> <p><b>DFO/DFP:</b> DFO 20 - 60 mg/kg/day subcutaneously on 2 days a week (mean (SD) dose DFO for the 29 participants who completed the trial at baseline: 36.0 (5.8) mg/kg/day and at end of trial: 33.3 (6.64) mg/kg/day) with DFP 25 mg/kg/ body weight 3 x daily for 5 days a week)</p>
Outcomes	<p><b>Adherence</b> see compliance below</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. SF change at 1 year</li> <li>2. LIC (measured by SQUID) change at 1 year</li> <li>3. ALT</li> <li>4. FBC</li> <li>5. Zinc levels</li> </ol>

	6. AEs 7. Participant compliance: compliance with DFP was assessed by pill counts, diary cards and an electronic cap that recorded the time and date of each opening of the tablet container. Compliance with DFO was assessed by diary cards, weekly physical examination of infusion sites, and by the Crono™ infusion pump that recorded the number of completed infusions Primary outcome: not identified	
Identification	Source of funding: Apotex Research Inc, Toronto, Canada. The last author of the study is an Apotex employee	
Notes	The trial inferred that participants had previously received DFO treatment but no details as to dose, schedule or duration were reported Sample-size calculation not reported	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken
Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about how treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	Unclear risk	The authors did not report any information as to whether participants, personnel or outcome assessors were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although 1 participant in the treatment group was withdrawn due to intolerance to DFP, this is unlikely to effect the findings of the trial
Selective reporting (reporting bias)	Unclear risk	Compliance to DFP was pre-specified as an outcome but was not measured or reported in the manuscript
Other bias	Low risk	The trial appears to be free of other sources of bias

Methods	<p><b>Study design:</b> single-centre RCT</p> <p><b>Study grouping:</b> parallel group</p> <p>Trial duration: September 2014 to September 2015</p>
Participants	<p><b>Baseline characteristics</b></p> <p><b>DFX</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 30</li> <li>• Age mean (SD): 8.9 (2.2)</li> <li>• Sex male/female: 9/21</li> <li>• Thalassaemia genotype (%): <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ng/mL) median (range): 3216 (2100 - 5862)</li> <li>• Previous iron chelation: 100%</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g): not reported</li> <li>• Splenectomy n (%): 4 (13.3)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/dL mean (SD): 85 (12)</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 30</li> <li>• Age mean (SD): 9.7 (1.9)</li> <li>• Sex male/female: 10/20</li> <li>• Thalassaemia genotype (%): <math>\beta</math>-thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ng/mL) median (range): 2773 (1980 - 4884)</li> <li>• Previous iron chelation: 100%</li> <li>• Duration of any iron chelation: not reported</li> <li>• LIC (mg/g): not reported</li> <li>• Splenectomy n (%): 17 (56.7)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/dL mean (SD): 7.9 (2.4)</li> </ul> <p><b>Inclusion criteria:</b> transfusion-dependent <math>\beta</math>-thalassaemia major, ages were <math>\geq 6</math> years, and they had SF levels greater than 1500 <math>\mu\text{g/L}</math> and were on irregular subcutaneous DFO chelation therapy</p> <p><b>Exclusion criteria:</b> serum creatinine above the upper age-related normal range, significant proteinuria (urinary protein/creatinine ratio 1.0 in a non-first-void urine sample at baseline), elevated ALT more than 3-fold of the ULN, GI diseases, clinically relevant auditory and/or ocular toxicity related to iron chelation therapy, cardiac disease, and/or SAEs with DFO or DFX, and absolute neutrophilic count 1500/mm<sup>3</sup> or platelet count 100,000/mm<sup>3</sup></p> <p><b>Pre-treatment:</b> significant difference between the 2 groups with participants having splenectomy 4 in DFX group compared to 17 in DFO group (<math>P = 0.001</math>), hepatitis C status 2 in DFX group compared to 11 in DFO group (<math>P = 0.005</math>) and baseline ALT baseline mean of 28.2 in the DFX group compared to 46.1 in the DFO group (<math>P = 0.001</math>)</p>
Interventions	<p><b>DFX</b></p> <ul style="list-style-type: none"> <li>• DFX was administered orally as a single daily dose of 20 - 40 mg/kg/day on an empty stomach after dissolution in water, apple juice, or orange juice to assure adequate bioavailability. Starting dose of DFX was individualized based on the frequency of blood transfusions</li> </ul> <p><b>DFO</b></p>

	<ul style="list-style-type: none"><li>DFO was administered at 20 - 50 mg/kg/day via subcutaneous infusion over 8 - 10 hours, 5 days per week</li></ul> 7-day washout phase	
Outcomes	<b>Adherence</b> to iron chelation therapy rates During the study, we kept records of all dosages administered, all study medications that were dispensed and returned, and intervals between visits to determine compliance with the treatment. The patients’ parents were instructed to contact the investigator if the patients were unable to take the study drug as prescribed <b>Trial-reported outcomes</b> 1. decrease in the SF level to < 1500 µg/L 2. Safety of the drugs that were used	
Identification	<b>Sponsorship source:</b> not stated <b>Country:</b> Egypt <b>Setting:</b> out-patient paediatric hematology clinic Al- Hussein University Hospital, Al-Azhar University, Cairo, Egypt <b>Comments:</b> no conflict of interest. <b>Authors name:</b> Dr Omar Atef Tolba <b>Institution:</b> Cairo University Children’s Hospital <b>Email:</b> omartolba80@yahoo.com <b>Address:</b> Dr Omar Atef Tolba, Cairo University Children’s Hospital, Department of Pediatrics, Cairo University, Egypt. Tel: +201222101717, +20233025539, Fax: +20233025539 There is no conflict of interest declared	
Notes	Sample-size calculation not reported	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote: “the patients were randomized in a 1:1 ratio based on permuted blocks to receive deferasirox (DFX) or deferoxamine (DFO) for one year.” Judgement comment: it is unclear risk as there is imbalance in the groups on several variables
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described and imbalance between groups
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: oral tablet versus subcutaneous infusion - unable to blind participants or personnel

Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Quote: "During the study, we kept records of all dosages administered, all study medications that were dispensed and returned, and intervals between visits to determine compliance with the treatment." Judgement Comment: Does not state if outcome assessors were blinded. Assessors would be aware the treatment participants were on
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no discontinuation of drugs or drop-out of follow-up occurred."
Selective reporting (reporting bias)	High risk	Quote: "Post-treatment levels of ALT and AST were significantly higher in the DFO group ( $p = 0.022$ , $p = 0.020$ , respectively), both drugs have comparable safety profiles, as the adverse effects noted did not reach clinical significance or lead to discontinuation of treatment with either agent. In the light of the comparable efficacy and safety of both agents for the reduction of iron overload, as was reported in the monotherapy of patients with transfusion-dependent thalassaemia (31, 32), the oral preparation merits convenience and therefore patient compliance and adherence to treatment regimen that needs to be taken on a long-term basis." "The oral DFX is recommended due to more convenience to assure adherence to treatment regimen." Judgement comment: the data within this trial do not provide evidence that DFX assures adherence. Pre-treatment ALT, AST were also higher in the DFO group - and also reflects imbalance in randomisation. Most outcomes vaguely reported (i.e. compliance - not percentages even though did a count and closely monitored). Also not clear if all drug-related AEs reported (i.e. agranulocytosis). Further the evidence is uncertain from this trial that both drugs of comparable efficacy and safety
Other bias	Unclear risk	Small trial $N = 60$ and short-term follow-up. Sample-size calculation not reported, and single-centre trial



Methods	<p><b>Study design:</b> multicentre RCT</p> <p><b>Study grouping:</b> parallel group</p> <p>Consecutive thalassaemia major participants (n = 275) were observed at the 25 SoSTE centres from September 30, 2000 to January 31, 2008</p> <p>9 participants did not meet inclusion criteria and 53 patients declined to participate. The remaining 213 participants were included; 105 and 108 respectively, were randomly allocated to DFP-DFO sequential treatment or DFP alone (Fig 1). None of the participants were lost to follow-up</p> <p><b>Study duration:</b> 5 year follow-up</p>
Participants	<p><b>Baseline characteristics</b></p> <p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 105</li> <li>• Age: mean (SD): 23 (8.0)</li> <li>• Sex: N (%): F: 55 (50.9)</li> <li>• Thalassaemia genotype (%): thalassaemia major (100%)</li> <li>• Baseline ferritin levels (ng/mL): mean (SD): 1727 (669)</li> <li>• Previous iron chelation: N = 105</li> <li>• Duration of any iron chelation: not stated</li> <li>• LIC (mg/g): mean SD: 4.6 (2.8)</li> <li>• Splenectomy: N (%): 17 (14.0)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: mean SD: 99 (10)</li> </ul> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: N = 108</li> <li>• Age: mean SD: 23 (7.8)</li> <li>• Sex: N (%): F: 66 (61.1)</li> <li>• Thalassaemia genotype (%): thalassaemia major (100%)</li> <li>• Baseline ferritin levels (ng/mL): mean (SD): 1868 (845)</li> <li>• Previous iron chelation: N = 108</li> <li>• Duration of any iron chelation: not stated</li> <li>• LIC (mg/g): mean (SD): 4.0 (2.3)</li> <li>• Splenectomy: N (%): 15 (12.7)</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: mean (SD): 98 (10)</li> </ul> <p><b>Inclusion criteria:</b> thalassaemia major, SF between 800 and 3000 ug/L over 13 years of age</p> <p><b>Exclusion criteria:</b> known intolerance treatment, platelet count <math>100 \times 10^9/l</math> or leucocyte count <math>3.0 \times 10^9/l</math>, severe liver damage, heart failure</p>
Interventions	<p><b>DFP/DFO</b></p> <ul style="list-style-type: none"> <li>• DFP 75 mg/kg, divided into 3 oral daily doses, for 4 days/week and DFO subcutaneous infusion (8-12 hours) at 50 mg/kg per day for the remaining 3 days/week</li> </ul> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• DFP alone, at the same dosage (75 mg/kg divided into 3 oral daily doses), administered 7 days a week</li> </ul>
Outcomes	<p><b>Adherence</b></p> <p>Compliance was assessed by counting the pills in each returned bag of DFP and by</p>

	assessing the number of infusions of DFO registered on the electronic pump <b>Trial-reported outcomes</b> 1. Difference between multiple observations of SF concentrations during the 5-year treatment. A correlation between LIC and SF levels has previously been shown in cohort of people with thalassaemia major treated with DFP (Olivieri et al, 1995) 2. Survival analysis 3. AEs 4. Costs 5. Multislice-multiecho T2* MRI scan, available since June 2004, was used in a subgroup of participants to evaluate variations in the iron content of the heart and liver during the trial	
Identification	<b>Sponsorship source:</b> Italian Society for the Study of Thalassaemia and Haemoglobinopathies (SoSTE) <b>Country:</b> Italy <b>Setting:</b> 25 SoSTE centres in Italy <b>Comments:</b> NCT 00733811 <b>Authors name:</b> Aurelio Maggio <b>Institution:</b> A.O.V. Cervello, U.O.C. di Ematologia <b>Email:</b> aureliomaggio@virgilio.it <b>Address:</b> A.O.V. Cervello, U.O.C. di Ematologia II,Cervello”, Palermo, Italy	
Notes	Follow-up was planned for 5 years; however, because of the beneficial effects, in terms of SF levels reduction in the sequential DFP-DFO group, observed after the interim analysis performed at 31 January 2008 the trial was stopped before the planned 5 years of treatment were completed for all participants years but mean (SD) duration of treatment was 2.5 (2.2) and 2.9 ( 2.1) years for DFP and sequential DFP-DFO groups, respectively Sample-size calculation reported	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote: “The randomization sequence was based on a computer-randomized list in permuted blocks of 10 with a 1:1 ratio,” Judgement comment: the randomization sequence was based on a computer-randomized list in permuted blocks of 10 with a 1:1 ratio. The sequence was concealed until interventions were assigned. Randomization was performed per each consecutive participant after verification of the exclusion criteria
Allocation concealment (selection bias)	Low risk	Quote: “To ensure allocation concealment, treatment was assigned by telephone contact from the coordinating centre”

Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Trial was open-label
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "All outcome assessments were done under code by physicians blinded to the trial treatment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The statistical analysis was based on the 'intention-to-treat' principle. None of the participants were lost to follow-up. However, SF measurements were only complete for all participants in the first year of the trial and decrease substantially thereafter to $n = 32$ in the combined group and $n = 26$ in the DFP group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	"Only 21 (35%) subjects in the DFP-alone and 12 (24%) in the sequential DFP-DFO group withdrew definitely from the trial (Table V). The mean time for definitive withdrawal was $152 \pm 103$ (days) in DFP-alone versus $112 \pm 76$ (days) in the sequential DFP-DFO group respectively." "The planned duration of treatment was 5 years. However, because of the beneficial effects, in terms of serum ferritin levels reduction in the sequential DFP-DFO group, observed after the interim analysis performed at January 31, 2008 the trial was stopped before the planned 5 years of treatment were completed for all patients. Therefore, the mean duration of treatment was $2.5 \pm 2.2$ and $2.9 \pm 2.1$ years for DFP and sequential DFP-DFO group respectively" Judgement comment: withdrawal rate is high and the trial stopped early

**Mourad 2003**

Methods	2-arm parallel RCT. Number of centres: 1. Trial dates: not stated. Duration of treatment: 1 year. Follow-up: none. Trial undertaken: Chronic Care Centre, Beirut, Lebanon.	
Participants	Number randomised: 25 (treatment group: 14; comparator group: 11) Number analysed: 25 (treatment group: 14; comparator group: 11) $\beta$ -thalassaemia participants, severely iron overloaded and previously poorly chelated Age range: 12 - 40 years Sex: treatment: 43% male, comparator: 64% male Ethnicity: not stated	
Interventions	<b>DFO</b> <ul style="list-style-type: none"><li>DFO by subcutaneous injection, 40 - 50 mg/kg 8 - 12 hours a day, 5 - 7 days/week</li></ul> <b>DFP/DFO</b> <ul style="list-style-type: none"><li>DFP 75 mg/kg/day orally in 3 divided doses, 7 days a week, DFO by subcutaneous injection, daily dose of 2 g over 8 - 12 hours, 2 days a week</li></ul>	
Outcomes	<b>Adherence</b> see compliance below <b>Trial-reported outcomes</b> <ol style="list-style-type: none"><li>Mean serum iron concentration at baseline, 6 &amp; 12 months (primary outcome)</li><li>Number RBC units during the trial</li><li>Iron excretion at 1 &amp; 12 months</li><li>Hb level measured weekly for 3 months then monthly for 9 months</li><li>Liver function measured weekly for 3 months then monthly for 9 months</li><li>Renal function measured weekly for 3 months then monthly for 9 months</li><li>Side effects</li><li>Participant compliance: compliance was assessed by the number of vials of DFX or tablets of DFP used. Safety was determined by detailed clinical and laboratory examination. Participants were also asked to complete questionnaires about any side-effects they experienced</li></ol>	
Identification	Source of funding: not stated.	
Notes	Prior exposure to iron chelators: DFO, less than 4 times a week, dose and duration not reported Sample-size calculation not reported	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken

**Mourad 2003** (Continued)

Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about how treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	Unclear risk	The authors did not report any information as to whether participants, personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis for all outcomes: there were no missing outcome data
Selective reporting (reporting bias)	High risk	Data for 2 pre-specified outcomes were not reported in the paper: iron excretion at 1 and 12 months and renal function. Both are important clinical markers of the efficacy of iron chelation therapy
Other bias	Low risk	The trial appears to be free of other sources of bias

**Olivieri 1997**

Methods	<p>2-arm parallel RCT</p> <p>Number of centres: 2</p> <p>Trial dates: November 1993 - September 1995</p> <p>Duration of treatment: analysis undertaken after 24 months (mean (SD) duration 33 (1.0) months, range 24 - 43 months)</p> <p>Follow-up: none</p> <p>Trial undertaken: Hospital Centres in Toronto and Montreal, Canada. These data are from the Toronto participants only</p>
Participants	<p><b>Baseline characteristics</b></p> <p>Number randomised: 64 (DFO: 32; DFP: 32)</p> <p>Number analysed: 37 (DFO: 18; DFP: 19). The trial reports details for why 6 and 7 participants respectively were not included in the analysis. The remaining participants had not completed 24 months treatment at the time of analysis for this trial report</p> <p><b>DFP (L1)</b></p> <ul style="list-style-type: none"> <li>• Age: not reported</li> <li>• Sex: F: 11; M: 14</li> <li>• Thalassaemia genotype (%): thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ng/mL) mean (SD): 2194 (1251)</li> <li>• Previous iron chelation: not reported</li> </ul>

	<ul style="list-style-type: none"> <li>• Duration of any iron chelation (duration of treatment in this trial - mean (SD) months): 11.0 (4.2) range 2 - 15</li> <li>• LIC (mg/g): 9.56 (4.77) Range 2.7 - 21.7</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Age: not reported</li> <li>• Sex: F: 11 M: 14</li> <li>• Thalassaemia genotype (%): thalassaemia major: 100%</li> <li>• Baseline ferritin levels (ng/mL) mean (SD): 2089 (048)</li> <li>• Previous iron chelation: Not reported</li> <li>• Duration of any iron chelation (duration of treatment in this trial - mean (SD) months): 11.63 (3.26), range 2 - 15 months</li> <li>• LIC (mg/g): 7.43 (3.59), range 2.4 - 15.7</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>Inclusion criteria:</b> diagnosed with homozygous <math>\beta</math>-thalassaemia, 10 years of age or older, willing to participate in the trial</p> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• refusal to participate in the screening</li> <li>• previously treated with DFP</li> <li>• serious adverse reactions to DFO</li> <li>• failed to attend 20% of the visits in the first 3 months of the trial</li> <li>• receiving other investigational drugs</li> <li>• past history of malignancy</li> <li>• medical, psychological or psychiatric risk</li> <li>• therapy with an investigational drug would be unwise</li> <li>• were pregnant or breast feeding</li> <li>• not using a reliable birth control method</li> </ul> <p><b>Pre-treatment:</b></p> <ul style="list-style-type: none"> <li>• stratified into high (7 mg Fe/g dry weight liver tissue) and low iron-overloaded (7 mg Fe/g dw) according to their hepatic iron concentration as assessed either by liver biopsy or a SQUID (or both)</li> <li>• 8 participants have been withdrawn from the study due to AEs (2), family reasons (1), psychiatric disorder (1), chronic neutropenia prior to starting on DFP (2), bone marrow transplantation (1) and non compliance with the trial protocol (1)</li> <li>• 25 participants on DFP and 26 participants on DFO have been used in the present analysis.</li> <li>• Author goes on to report that results of n = 5 in DFO were not evaluated as there was no compliance data. A further n = 5 participants on DFP and n = 2 were excluded for the analysis of the correlation between compliance + successful outcome (as measured by LIC) as there were 6 months of data available. Therefore, for the main outcome the actual N = 39 (n = 20 in DFP and n = 19 in DFO)</li> </ul>
Interventions	<p><b>DFP (L1)</b></p> <ul style="list-style-type: none"> <li>• DFP 75 mg/kg/day in 3 divided doses</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• DFO 50 mg/kg/night, 4 - 7 night/week</li> </ul>

Outcomes	<b>Adherence</b> see adherence below <b>Trial-reported outcomes</b> 1. Change in LIC (measured by SQUID or biopsy) between 12 months prior to randomisation & 24 months duration on trial treatment 2. 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 3 months	
Identification	<b>Sponsorship source:</b> no sponsorship stated <b>Country:</b> Canada <b>Setting:</b> Transfusion Clinic <b>Authors name:</b> Nancy Olivieri <b>Institution:</b> University of Toronto <b>Source of funding:</b> not stated	
Notes	Prior exposure to iron chelators: not reported Abstract publication. Some data from Pope 1995 thesis included for baseline characteristics Sample-size calculation not reported	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	High risk	Quote: “After stratification patients by LIC (>7mg Fe/g; < 7mg Fe/g) ’patients were assigned by a research pharmacist who did not know the patients”
Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about how treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	1 treatment a pump and 1 treatment a tablet, participants and researchers would not be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial analysed data from 58% of randomised participants. Of the 42% randomised participants who were not available for outcome analysis: • 22% randomised participants had not

**Olivieri 1997** (Continued)

		<p>completed the required 24 months treatment at the time of analysis for this trial report;</p> <ul style="list-style-type: none"> <li>• 16% DFP-treated participants and 5% DFO treated participants were withdrawn due to treatment induced side effects</li> </ul> <p>This missing data may inappropriately affect the statistical findings of the trial</p>
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified were reported in the manuscript
Other bias	Unclear risk	The trial was reported in an abstract, thus there are few data available to make an assessment of whether the trial was free of other bias. Trial stopped early by manufacturer

**Pennell 2006**

Methods	<p>2-arm parallel RCT</p> <p>Number of centres: 4</p> <p>Trial dates: December 2002 - March 2005</p> <p>Duration of treatment: 1 year</p> <p>Follow-up: outcome data recorded for duration of treatment</p> <p>Trial undertaken: 4 participating centres in Italy and Greece</p>
Participants	<p>Number randomised: 61 DFO: 32; DFP: 29</p> <p>Number analysed: variable across outcomes. Minimum and maximum numbers analysed were: treatment group: 30 - 32; comparator group: 27 - 29. Trial reported details as to why data from 1 participant in the treatment group and 2 in the comparator group were withdrawn from treatment</p> <p>Transfusion-dependent homozygous participants with <math>\beta</math>-thalassaemia major</p> <p>Age: mean (SD) treatment group: 26.2 (4.7) years; mean (SD) comparator group: 25.1 (5.8) years</p> <p>Sex: treatment group: 50% male; comparator group: 52% male</p> <p>Ethnicity: Greek/Italian: treatment group: 18/14; comparator group: 16/13</p>
Interventions	<p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• DFO by subcutaneous injection, 50 mg/kg for 5 or more days a week</li> </ul> <p><b>DFP</b></p> <ul style="list-style-type: none"> <li>• DFP initial dose 75 mg/kg/day increasing to 100 mg/kg/day. Mean actual dose: 92 mg/kg/day</li> </ul>
Outcomes	<p><b>Adherence rates:</b> DFP compliance was measured using the Medication Event Monitoring System device (Aardex, Zug, Switzerland) and calculated as the percent of openings with an interval longer than 4 hours recorded, divided by number of doses prescribed. DFO compliance was calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed</p>



	<b>Trial-reported outcomes</b> 1. Change over 1 year in myocardial T2* (primary outcome) 2. Cardiac volumes and function 3. LIC 4. SF 5. ANC 6. AEs 7. ALT 8. Serum zinc levels 9. Serum creatinine levels	
Identification	Trial sponsor: Apotex (manufacturer of DFP)	
Notes	Prior exposure to iron chelators: DFO at a mean (SD) dose of 39 (8) mg/kg/day for 5 - 7 days/week Sample-size calculation reported	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken
Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about whether treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Open label one treatment subcutaneous and the other oral so not possible to mask treatments
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	The primary outcome was independently measured in a different country (UK) to where the trial took place and the findings were not communicated back to the clinicians during the course of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis of the outcomes SF and AEs Data from 1 participant in the treatment (DFO) group were not included in the analysis of the cardiac outcomes (primary outcome) and last observation carried forward method was used to accommodate the missing data from 3 other participants (1 treatment group and 2 from the comparator group) in the cardiac outcomes (pri-

**Pennell 2006** (Continued)

		mary outcome) 2 participants in each treatment group did not have a LIC assessment at 12 months and the data from these participants were missing from the analysis
Selective reporting (reporting bias)	High risk	The following pre-specified outcomes were not reported in the manuscript: ANC; ALT; serum zinc levels; and serum creatinine levels
Other bias	High risk	There are several imbalances in baseline characteristics between the 2 interventions including a major imbalance in SF measures with the DFO group having much higher levels as well as a greater proportion of participants with severe iron overload (above 2500 µg/L)

**Pennell 2014**

Methods	<p><b>Study design:</b> RCT</p> <p><b>Study grouping:</b> parallel group</p> <p>CORDELIA was a prospective, multinational, randomised, open-label, parallel-group, phase 2 trial. A total of 81.2% of participants (n = 160) completed 1 year of treatment</p>
Participants	<p>“Overall, 925 patients were screened and 197 randomized. The majority of patients screened were <math>\beta</math>-thalassemia major patients (902/925; 99.1%). Other patients who were screened and for whom underlying anaemia was captured had low/intermediate 1 myelodysplastic syndrome (n = 4), Diamond-Blackfan anaemia, <math>\beta</math>-thalassemia intermedia, congenital dyserythropoietic anaemia, and paroxysmal nocturnal haemoglobinuria (all n = 1). Only <math>\beta</math>-thalassemia major patients fulfilled the inclusion criteria and were enrolled in the study. A total of 81.2% of patients (n = 160) completed 1 year of treatment”</p> <p><b>Baseline characteristics</b></p> <p><b>DFX (Exjade)</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 98</li> <li>• Age mean (SD): 19.9 (6.5)</li> <li>• Sex (M:F ratio n): 58:40</li> <li>• Thalassaemia genotype (%): thalassaemia major: 100%</li> <li>• Previous iron chelation: DFO: 41 (42.7); DFP: 9 (9.4); DFO + DFP: 21 (21.9); DFX: 18.1(8.8); Unknown or irregular: 7(7.3)</li> <li>• Duration of any iron chelation mean (SD) years: 14.0 (7.0)</li> <li>• LIC (mg Fe/g dw): &lt; 7: 11 (12.1); 7 to &lt; 15: 14 (15.4); <math>\geq 15</math>: 66 (72.5)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Median SF (range), ng/mL (per protocol population): 5062 (613 - 15331)</li> </ul> <p><b>DFO (Desferal)</b></p>

	<ul style="list-style-type: none"> <li>• Total # of participants: 99</li> <li>• Age mean (SD): 19.7 (6.3)</li> <li>• Sex (M:F ratio n): 57:42</li> <li>• Thalassaemia genotype (%): thalassaemia major: 100%</li> <li>• Previous iron chelation: DFO: 39 (42.9); DFP: 5 (5.5); DFO + DFP: 21 9 (23.1); DFX: 23 (25.3); Unknown or irregular: 3 (3.3)</li> <li>• Duration of any iron chelation mean (SD) years: 14.3 (7.2)</li> <li>• LIC (mg Fe/g dw): 7: 8 (9.9); 7 to 15: 14 (17.3); <math>\geq 15</math>: 59 (72.8)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> <li>• Median SF (range), ng/mL (per protocol population): 4684 (677 - 13342)</li> </ul> <p><b>Inclusion criteria:</b> people with <math>\beta</math>-thalassaemia major, Diamond-Blackfan anaemia, low/intermediate myelodysplastic syndromes, or sideroblastic anaemia, aged <math>\geq 10</math> years with myocardial T2* 6 - 20 ms, LVEF <math>\geq 56\%</math>, R2 MRI LIC <math>\geq 3</math> mg Fe/g dw, lifetime history of <math>\geq 50</math> units RBC transfusions, and receiving <math>\geq 10</math> unit/year of RBC transfusions</p> <p><b>Exclusion criteria:</b> participants with serum creatinine above the ULN or significant proteinuria (urinary protein/creatinine ratio <math>\geq 1.0</math> mg/mg in a non-first-void urine sample at baseline; people with ALT 5 x the ULN only if their LIC was 10 mg Fe/g dw; considerable impaired GI function or GI disease; history of clinically relevant ocular and/or auditory toxicity related to iron chelation; therapy, and history of HIV seropositivity or malignancy within the past 5 years; clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnoea, exercise intolerance, lower-extremity edema, arrhythmias)</p>
Interventions	<p><b>DFX (Exjade)</b></p> <ul style="list-style-type: none"> <li>• Once-daily DFX starting dose was 20 mg/kg per day for 2 weeks, followed by 30 mg/kg per day for 1 week, and then continued with 40 mg/kg per day</li> </ul> <p><b>DFO (Desferal)</b></p> <ul style="list-style-type: none"> <li>• An intensified dosing regimen of DFO was administered at 50 to 60 mg/kg per day via subcutaneous infusion over 8 - 12 hours, 5 - 7 days a week, in accordance with Thalassaemia International Federation Guidelines</li> </ul> <p>Mean actual dose over 1-year treatment was 36.7 6 4.2 mg/kg per day DFX (range, 19.7- 43.3 mg/kg per day). Mean actual dose of DFO was 41.5 6 8.7 (13.2 - 60.2) mg/kg per day, when normalized to a 7-day regimen</p>
Outcomes	<p><b>Adherence</b> to iron chelation therapy rates: not stated how adherence was measured</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. Ratio of Gmean myocardial T2* after 1 year of treatment with DFX divided by the ratio of Gmean for DFO</li> <li>2. Change in LVEF after 1 year of treatment, assessed by absolute change from baseline CMR</li> <li>3. Absolute change from baseline in LIC after 1-year treatment</li> <li>4. Absolute change from baseline in SF after 1-year treatment</li> </ol>
Identification	<p><b>Sponsorship source:</b> Novartis Pharma AG</p> <p><b>Country:</b> multinational, 11 countries</p> <p><b>Setting:</b> 22 centres across 11 countries</p> <p><b>Comments:</b> the authors thank Debbi Gorman of Mudskipper Business Ltd for medical editorial assistance. Financial support for medical editorial assistance was provided by</p>

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Notes	Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. Novartis Pharmaceuticals Corporation also collaborated with the external authors to assist in the development and approval of the manuscript for publication	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote: "22 centers across 11 countries. Following a 35-day screening phase, patients were randomized in a 1:1 ratio" Randomisation was based on permuted blocks; stratification by centre was not conducted
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment except that randomisation was based on permuted blocks
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: open-label trial - subcutaneous pump versus oral tablet - difficult to blind
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "Core laboratories were blinded to treatment allocation. In order to eliminate potential unrecognized biases, the core clinical trial team was blinded to the treatment assignment prior to the database lock for the primary analysis."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 21 withdrawn DFO arm 16 in DFX (78 to 82 completed trial) Efficacy outcomes reported in per protocol and safety in the participants who received the trial drug
Selective reporting (reporting bias)	Unclear risk	Investigator-reported AEs, regardless of causality, were reported in 65 (67.7%) DFX participants and 69 (75.8%) DFO participants (supplemental Table 2). AEs

		<p>suspected to be related to trial drug occurred in 35.4% of DFX participants and 30.8% of DFO participants</p> <p>Judgement comments: It is unclear if investigator-reported AEs and those suspected to be related to trial drug include the same AEs. Also, they only report the end of trial LIC value for the DFX group</p>
Other bias	Low risk	The trial appears to be free of other sources of bias

## Taher 2017

Methods	<p><b>Study design:</b> multicentre RCT conducted in several countries</p> <p><b>Study grouping:</b> parallel group</p> <p><b>Study duration:</b> 24 weeks</p>
Participants	<p><b>Baseline characteristics</b></p> <p><b>DFX film-coated tablet</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: N = 87</li> <li>• Age: 34.6 (19.97)</li> <li>• Sex: F: 41</li> <li>• Thalassaemia genotype N (%): thalassaemia major: 70 (80.5)</li> <li>• Previous iron chelation: 79 (90.8)</li> <li>• Median SF (range), ng/mL: 2983 (939 - 8250)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>DFX dispersible tablet</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: N = 86</li> <li>• Age: 35.1 (18.60)</li> <li>• Sex: F: 47</li> <li>• Thalassaemia genotype N (%): thalassaemia major: 70 (81.4)</li> <li>• Baseline ferritin levels (ng/mL) mean (SD): 2089 (048)</li> <li>• Previous iron chelation: 77 (89.5)</li> <li>• Median SF (range), ng/mL: 2485 (915 - 8250)</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL mean (SD): not reported</li> <li>• Hb, g/L: not reported</li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Males and females aged <math>\geq 10</math> years</li> <li>• Transfusion-dependent thalassaemia and iron overload, requiring DFX dispersible tablet at doses of <math>\geq 30</math> mg/kg/day as per the investigator's decision or participants with very low, low or intermediate (int) risk myelodysplastic syndrome and iron overload, requiring DFX dispersible tablet at doses of <math>\geq 20</math> mg/kg/day as per the investigator's decision</li> <li>• History of transfusion of at least 20 PRBC units and anticipated to be transfused</li> </ul>

	<p>with at least 8 units of PRBCs annually during the study</p> <ul style="list-style-type: none"> <li>SF &gt; 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria).</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine at screening Visit 1 and screening Visit 2 and the mean value will be used for eligibility criteria</li> <li>Serum creatinine &gt; 1.5 x ULN at screening measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria)</li> <li>ALT (SGPT) &gt; 5 x ULN, unless LIC confirmed as &gt;10 mg Fe/dw within 6 months prior to screening visit 1. Significant proteinuria as indicated by a urinary protein/creatinine ratio &gt; 0.5 mg/mg in a non-first void urine sample at screening Visit 1 or screening Visit 2</li> <li>Participants with significant impaired GI function or GI disease that may significantly alter the absorption of oral DFX (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection)</li> <li>Liver disease with severity of Child-Pugh Class B or C</li> </ul>
Interventions	<p><b>DFX film-coated tablets</b></p> <ul style="list-style-type: none"> <li>DFX film-coated provided as 90 mg, 180 mg and 360 mg film-coated tablets for oral use</li> </ul> <p><b>DFX dispersible tablet</b></p> <ul style="list-style-type: none"> <li>DFX dispersible tablet provided as 125 mg, 250 mg and 500 mg dispersible tablets for oral use</li> </ul>
Outcomes	<p><b>Adherence to iron chelation therapy rates</b></p> <p>Compliance with medication as assessed by relative consumed tablet count</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>Overall safety of both DFX formulations, measured by frequency and severity of AEs and changes in laboratory values from baseline to 24 weeks</li> <li>Evaluation of both formulations on selected GI AEs (diarrhoea, constipation, nausea, vomiting, and abdominal pain) during treatment</li> <li>Estimation of treatment compliance</li> <li>Evaluation of both formulations on participant satisfaction, palatability, and GI symptoms using PROs</li> <li>Evaluation of the pharmacokinetics of both formulations</li> <li>Reported % compliant with upper and lower percentages</li> </ol>
Identification	<p><b>Sponsorship source:</b> Novartis Pharmaceuticals</p> <p><b>Country:</b> USA</p> <p><b>Comments:</b> NCT02125877</p> <p><b>Authors name:</b> Ali Taher</p> <p><b>Institution:</b> American University of Beirut Medical Center</p> <p><b>Email:</b> ataher@aub.edu.lb</p> <p><b>Address:</b> Haematology and Oncology, Department of Internal Medicine, Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon</p>
Notes	<p>Sample-size calculation not reported</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>"Randomization was stratified by underlying disease and previous chelation treatment."</p> <p>No clear description of randomisation or if participants were randomised centrally</p>
Allocation concealment (selection bias)	High risk	<p>Quote: "Post- hoc analyses identified that 23 patients on FCT (26%) were started on a dose that was higher than recommended in the protocol compared with 8 patients (9.3%) on DT (not recognized or reported by the investigators as dosing error)."</p> <p>Judgement comment: the trial was open label and most participants had been on 1 or the other of the trial drugs prior to the trial - doses may have corresponded to prior dosing since there was no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: open-label
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	No description of how outcome assessment was performed - centrally or blinded open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Quote: "Overall, all patients were satisfied with their medicine during the study period; satisfaction scores were higher with deferasirox FCT compared with DT at all visits."</p> <p>Judgement comment: no data provided on number of participants or scores just general statements</p>
Selective reporting (reporting bias)	High risk	<p>Quote: "patients discontinued treatment because of AEs (n = 10), protocol deviation (n = 5), withdrawal of consent (n = 3), patient guardian decision (n = 2), and other reasons (administrative problems, death, and physician's decision, n = 1 each)."</p>

		Judgement comment: investigators do not report all outcomes by treatment assignment, and AEs and SAEs are reported as suspected relationship to trial drug and occurring in > or equal to 10%
Other bias	Unclear risk	<p>“The absolute reduction in median serum ferritin (range) in patients receiving FCT was -350 (-4440-3572) ng/mL and in those receiving DT was -85.5 (-2146-8250) ng/mL); these correspond to a relative change of -14.0% with FCT and -4.1% with DT.”</p> <p>Judgement comment: some of difference in change could be accounted for more participants starting on a higher dose of film-coated tablet</p>

## Tanner 2007

Methods	2-arm parallel RCT Number of centres: multicentre (12 centres) Duration of treatment: 12 months Follow-up: not stated Trial undertaken: thalassaemia out-patient clinics in Sardinia
Participants	Number randomised: 65 (treatment group: 33; comparator group: 32) Number analysed: not reported Number completing treatment: 60 (treatment group: 32; comparator group: 28). The reason for the withdrawal was not fully reported by the trial authors Participants aged 18 years or older with a diagnosis of $\beta$ -thalassaemia, currently maintained on subcutaneous DFO and with a myocardial T2* between 8 - 20 ms Age: treatment group: mean (SD) 28.7 (5.3) years; comparator group: mean (SD) 28.8 (4.2) years Age range for both arms was 18 - 42 years Sex: treatment group: 39% male; comparator group: 44% male Ethnicity: not stated
Interventions	<b>DFO</b> <ul style="list-style-type: none"> <li>DFO 40 - 50 mg/kg subcutaneously for 5 days a week (DFO actual dose: 43.4 mg/kg for 5 days) with an oral placebo (no further details reported)</li> </ul> <b>DFO/DFP</b> <ul style="list-style-type: none"> <li>DFO 40 - 50 mg/kg subcutaneously for 5 days a week (DFO actual dose: 34.9 mg/kg for 5 days) with DFP 75 mg/kg daily for 7 days a week</li> </ul>
Outcomes	<b>Adherence</b> see compliance below <b>Trial-reported outcomes</b> <ol style="list-style-type: none"> <li>Change over 1 year in myocardial T2* (primary outcome)</li> <li>Change in liver T2* at 12 months</li> <li>SF</li> </ol>



	4. Left ventricular volume & function 5. Brachial artery reactivity as a marker of heart failure 6. Participant compliance with chelation treatments: DFO compliance was calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed. DFP/placebo compliance was measured through pill counting at the bi-monthly visits 7. AEs 8. BNP test	
Identification	Source of funding: CORDA, Royal Brompton & Harefield Hospitals Charitable funds, Cooley’s Anemia Foundation, Apotex, UK Thalassaemia Society, University College London Special trustees Chairty	
Notes	Prior exposure to iron chelation: DFO mean (SD) dose 36.4 (11.1) mg/kg per day for 5.5 day/week (equivalent to 40.5 mg/kg for 5 day/week). Participants were excluded if they had previously received DFP Sample-size calculation reported	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken
Allocation concealment (selection bias)	High risk	Trial reports that the participants and clinicians were aware of how treatment was to be allocated
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	Unclear risk	The authors did not report any information as to whether participants or personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	As the trial does not report the number of participants included in each outcome assessment. The trial reports the number completing treatment and the reasons why 3 participants in the treatment group (1 adverse event & 2 participant requests) and 4 participants in the comparator group (3 adverse events & 1 participant request) were withdrawn from the trial

**Tanner 2007** (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes pre-specified were reported in the manuscript
Other bias	Low risk	The trial appears to be free of other sources of bias

**Vichinsky 2007**

Methods	<p><b>Study design:</b> RCT</p> <p><b>Study grouping:</b> parallel group</p> <p>The study duration was 52 weeks. Participants were recruited by investigators at 44 sites in the USA, France, Italy, UK and Canada</p>
Participants	<p><b>Baseline characteristics</b></p> <p><b>DFX</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 132</li> <li>• Age: 15 range 3 - 54</li> <li>• Sex (female %): 60.6</li> <li>• Sickle cell genotype N (%): 100</li> <li>• Baseline ferritin levels (ng/mL) median (min - max): 3460 (1082 - 1201)</li> <li>• Previous iron chelation %: 62.9</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL mean (SD): not reported</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• Total # of participants: 63</li> <li>• Age: 16. Range 3 - 51</li> <li>• Sex (female %): 55.6</li> <li>• Sickle cell genotype N (%): 100</li> <li>• Baseline ferritin levels (ng/mL) median (min - max): 2834 (1015 - 15578)</li> <li>• Previous iron chelation %: 60.3</li> <li>• Splenectomy n (%): not reported</li> <li>• QoL (mean (SD)): not reported</li> </ul> <p><b>Age group (% DFX, DFO)</b></p> <p>&lt; 6 years: 3.0, 4.8</p> <p>6 to &lt; 12 years: 22.7, 23.8</p> <p>12 to &lt;16 years: 25.0, 20.6</p> <p>16 to &lt; 50 years: 47.7, 49.2</p> <p>50 to &lt; 65 years: 1.5, 1.6</p> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• People with SCD <math>\geq</math> to 2 years of age and with iron overload from repeated blood transfusions</li> <li>• People receiving regular blood transfusions or those sporadically transfused who received at least 20 units of packed RBCs or equivalent were eligible</li> <li>• Prior chelation therapy was permitted but was not mandatory</li> <li>• The serum ferritin level for entry into the screening period of this study was <math>\geq</math> 1000 <math>\mu</math>g/L</li> </ul> <p><b>Exclusion criteria</b></p>

	<ul style="list-style-type: none"> <li>• People were excluded if they had a serum creatinine above the ULN</li> <li>• Significant proteinuria (as indicated by a urinary protein:creatinine ratio of <math>\geq 0.5</math> confirmed at 2 visits)</li> <li>• Active hepatitis B or C</li> <li>• Second and third atrioventricular block, QT interval prolongation, or therapy with digoxin or similar medications</li> <li>• Treatment with beta blockers or angiotensin-converting enzyme inhibitors was permitted. Those with chelation therapy-associated ocular toxicity were excluded</li> </ul>
Interventions	<p><b>DFX</b></p> <ul style="list-style-type: none"> <li>• The initial 24 participants enrolled were randomised to receive DFX 10 mg/kg, all subsequent participants randomised to DFX were dosed at 10 - 30 mg/kg according to baseline LIC. DFX was given once daily each morning as a dispersed solution in water, half-an-hour before breakfast. The dose of DFX was reduced by 1 dose level and not re-escalated for participants 15 years and older if serum creatinine increased 33% above baseline on two consecutive occasions. For children less than 15 years of age, the dose was only decreased if these values were also above the age-appropriate ULN. DFX was interrupted for moderate or severe skin rash and re-instituted at half the initial dose, and dose re-escalation was permitted</li> </ul> <p><b>DFO</b></p> <ul style="list-style-type: none"> <li>• DFO was administered as a slow subcutaneous infusion over 8 - 12 hours using electronic Microject Chrono infusion pumps on 5 - 7 days a week. In order to facilitate the comparison of different schedules, all DFO doses reported were normalised to administration for 5 days/week (i.e. 50 mg/kg administered 7 days/week would be reported as 70 mg/kg)</li> </ul>
Outcomes	<p><b>Adherence to iron chelation therapy rates</b></p> <p>Compliance. For DFX, compliance was assessed by counting the number of tablets returned in bottles at each visit. For DFO, the numbers of vials returned at each visit were counted</p> <p><b>Trial-reported outcomes</b></p> <ol style="list-style-type: none"> <li>1. Safety assessments</li> <li>2. Laboratory assessments were performed at least monthly and included complete blood counts with differential counts. Biochemistry testing included electrolytes, glucose, liver function tests, gamma-glutamyl-transferase, lactate dehydrogenase, cholesterol, triglycerides, uric acid, total protein, C-reactive protein, copper and zinc levels. Iron parameters included total iron, transferrin, transferrin saturation and ferritin. Urinary testing performed on random collections included determination of creatinine, total protein and albumin</li> <li>3. Physical examinations, ECGs, audiometry and ophthalmological tests were performed at baseline, 12, 24, 36 and 52 weeks. In participants less than 16 years of age, additional assessments included growth velocity and pubertal stage</li> <li>4. Efficacy assessments. LIC was determined by SQUID biospectrometry at baseline, 24 and 52 weeks. The 24-week assessment was performed primarily for safety purposes, and the change in LIC was calculated between baseline and 52 weeks. SF was assessed monthly during the trial and the change was determined using the baseline and final ferritin level</li> </ol>

Identification	<b>Sponsorship source:</b> Novartis Pharmaceuticals <b>Country:</b> international (Canada, France, Italy, UK and USA) <b>Setting:</b> medical centre outpatient <b>Authors name:</b> Elliott Vichinsky <b>Institution:</b> Children's Hospital and Research Center at Oakland, <b>Email:</b> evichinsky@mail.cho.org <b>Address:</b> Children's Hospital and Research Center at Oakland, 747 52nd Street, Oakland, CA 94609, USA Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. Novartis Pharmaceuticals Corporation also collaborated with the external authors to assist in the development and approval of the manuscript for publication	
Notes	Sample-size calculation reported	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was performed using an interactive voice response system"
Allocation concealment (selection bias)	Unclear risk	Quote: "stratified according to the following age groups: 2 to < 6 years, 6 to < 12 years, 12 to < 16 years and 16 years and older. The randomisation sequence included permuted block groups of six patients for each of the three age strata." Judgement comment: some of the age groups had few participants and unclear if allocation would remain concealed with permuted block groups of 6 participants
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: no mention of blinding, but DFO is delivered by infusion pumps and DFX is a solution in water, so blinding not feasible
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Judgement comment: no description of blinding: Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. The data were analysed under supervision of the trial statistician and were reviewed by the investigators

Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported. 8 participants did not complete and were not included. 6 DFX arm withdraw consent, one in DFO arm. 3 DFO non compliant, 2 DFX and 1 DFO lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Quote: "Adverse events, irrespective of the relationship to study medication, which occurred in more than 10% of patients receiving either treatment, are shown in Table III. As arbitrarily defined by an increased frequency of at least 5% indicating a potential relationship to drug administration." Judgement comment: do not report the total number of AEs in all participants, as well there was a substantial number of participants experience SAEs and there is no list of the type except for pain crisis: The number of participants receiving DFX and DFO that reported SAEs was similar (46.2% and 42.9% respectively) and the most common SAE in both groups was sickle cell anaemia with crisis (33.3% and 31.7% respectively). Also table of AEs report % and no totals so impossible to determine total number of participants with an AE
Other bias	Unclear risk	Quote: "The reasons for withdrawal of consent were not included in the database." Quote: "The initial 24 patients enrolled were randomised to receive deferasirox 10 mg/kg or deferoxamine at recommended doses of 20-60 mg/kg based on initial LIC. Subsequently, additional safety information became available for deferasirox suggesting a need to modify the starting dose (Cappellini et al, 2006). Therefore, following the enrolment of the first 24 patients, the study was amended so that all subsequent patients randomised to deferasirox were dosed at 10-30 mg/kg according to baseline LIC" Judgement comment: it is important to understand reasons for withdrawals and also the nature of the missing safety information which may have implications for dosing and effects of the dosing amendment

ADRs: adverse drug reactions  
 AEs: adverse events  
 ALT: alanine aminotransferase  
 ANC: absolute neutrophil count  
 BNP: brain natriuretic peptide  
 CBC: complete blood count  
 CMR: cardiovascular magnetic resonance imaging  
 DFO: deferoxamine  
 DFP: deferiprone  
 DFX: deferasirox  
 dw: dry weight  
 ECGs: electrocardiograms  
 FBC: full blood count  
 Hb: haemoglobin  
 HRQoL: health-related quality of life  
 ICT: iron chelation therapies  
 IQR: interquartile range  
 LVEF: left ventricular ejection fraction  
 LIC: liver iron concentration  
 MRI: magnetic resonance imaging  
 PK: pharmacokinetic  
 PRBC: packed red blood cell  
 QoL: quality of life  
 RBCs: red blood cells  
 RCT: randomised controlled trial  
 SAEs: serious adverse events  
 SCr: sickle cell retinopathy  
 SD: standard deviation  
 SF: serum ferritin  
 SGPT: serum glutamate-pyruvate transaminase  
 SQUID: Superconducting Quantum Interference Device  
 UIE: urinary iron excretion  
 ULN: upper limit of normal  
 WBC: white blood count

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

Study	Reason for exclusion
<a href="#">Abu 2015</a>	Wrong study design - qualitative interview questionnaire used
<a href="#">Al Kloub 2014</a>	Wrong study design - qualitative interview questionnaire used
<a href="#">Al Kloub 2014a</a>	Wrong study design - cross-sectional study.
<a href="#">Al Refaie 1995</a>	Wrong study design - medication study - not an RCT.
<a href="#">Alvarez 2009</a>	Wrong study design - medication study - not an RCT.

(Continued)

<a href="#">Armstrong 2011</a>	No intervention.
<a href="#">Bala 2014</a>	No intervention.
<a href="#">Belgrave 1989</a>	No intervention.
<a href="#">Berkovitch 1995</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">Chakrabarti 2013</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">Daar 2010</a>	Wrong setting - single-centre study.
<a href="#">Gomber 2004</a>	No intervention.
<a href="#">Kidson Gerber 2008</a>	Wrong study design - clinical audit of medication use.
<a href="#">Kolnagou 2008</a>	Wrong study design - medication study not RCT.
<a href="#">Leonard 2014</a>	Wrong study design - single-treatment study.
<a href="#">Loiselle 2016</a>	Review.
<a href="#">Mazzone 2009</a>	Wrong comparator - healthy children not taking iron chelation therapy
<a href="#">NCT01709032</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">NCT01825512</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">NCT02133560</a>	Wrong study design - single-centre study with no control.
<a href="#">NCT02466555</a>	Wrong study design - single-centre study with no control.
<a href="#">Pakbaz 2004</a>	Wrong study design - single-centre study with no control.
<a href="#">Pakbaz 2005</a>	Wrong study design - single-centre study with no control.
<a href="#">Porter 2009</a>	Wrong study design - medication intervention not a RCT.
<a href="#">Porter 2012</a>	Wrong study design - medication intervention not a RCT.
<a href="#">Vichinsky 2005</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">Vichinsky 2008</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">Waheed 2014</a>	Not designed to measure adherence to iron chelation therapy.
<a href="#">Walsh 2014</a>	Review.

(Continued)

Yarali 2006	Not designed to measure adherence to iron chelation therapy.
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RCT: randomised controlled trial

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

### Antmen 2013

Methods	Prospective cohort study; parallel group
Participants	Participants using DFX - we do not know the disease diagnosis and therefore awaiting classification Exclusion criteria: not stated
Interventions	Educational intervention, standard care (as defined in the study)
Outcomes	Exjade Patient Compliance Program (EX-PAT) was established to increase patients' knowledge about DFX usage. This abstract aimed to represent the results of the pilot EX-PAT program It is highly recommended to educate the patients under iron chelating treatment about possible complication and usage of chelating agent
Notes	Email sent to author asking for the following information so we could include the study: a full study report of this abstract? If this is not available would it be possible to have more information on: 1. The disease diagnosis of the participants (were they sickle cell (phenotypes) or thalassaemia (phenotypes) or other); 2. How participants were assigned to intervention or control; 3. Any inclusion/exclusion criteria; 4. Any group differences; 5. Is the age range for the whole group or is it for the intervention group only? If so could we have the age range for the control group; 6. Baseline and end of study ferritin levels; 7. SAEs or any AEs

### NCT00004982

Methods	RCT; parallel group
Participants	Inclusion criteria: ages eligible for trial: 7 years and older (child, adult, senior); genders eligible for study: both Exclusion criteria: overt cardiac disease
Interventions	Combination iron chelation therapy, standard care (as defined in the trial)
Outcomes	This small trial is testing the premise that a combination of drugs as a new approach to iron chelation therapy may reduce side effects and increase efficacy. If both drugs can be given orally, there may be a better chance of finding a suitable alternative to Desferal. Several combinations of experimental iron chelating drugs are being used in this trial
Notes	This trial has been completed. Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) . No study results posted NCT00004982: scant information about the trial was documented on the clinicaltrials.gov web site. We have been unable to identify any publications from this trial and despite repeated emails to the trial co-ordinator and searching the funders web site, we have been unable to identify any further details about the trial. Start date: December 1998;



estimated completion November 2002
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AEs: adverse events

DFX: deferasirox

RCT: randomised controlled trial

SAEs: serious adverse events

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

### EudraCT 2012-000353-31

Trial name or title	Multicentre, randomised, open-label, non-inferiority active-controlled trial to evaluate the efficacy and safety of DFP compared to DFX in paediatric patients aged from 1 month to less than 18 years of age affected by transfusion-dependent haemoglobinopathies
Methods	Randomised trial, parallel group
Participants	<ol style="list-style-type: none"> <li>1. Children on current treatment with DFO or DFX or DFP in a chronic transfusion program receiving at least 150 mL/kg/year of packed RBCs (corresponding approximately to 12 transfusions);</li> <li>2. For those naive to chelation treatment: participants that have received at least 150 mL/kg of packed RBCs (corresponding to approximately 12 transfusions) in a chronic-transfusion program and with SF levels <math>\geq</math> 800 ng/mL;</li> <li>3. For children aged from 1 month to less than 6 years: known intolerance or contraindication to DFO;</li> <li>4. Written informed consent and patient's informed assent to child's maturity and understanding</li> </ol>
Interventions	DFP compared to DFX
Outcomes	<p>Percentage of successfully chelated children assessed by SF levels (all participants) and cardiac MRI T2* (children above 10 years of age able to have an MRI scan without sedation)</p> <ol style="list-style-type: none"> <li>1. LLC as measured by MRI in those able to undergo MRI scan without sedation</li> <li>2. Safety and tolerability assessments</li> <li>3. QoL</li> </ol>
Starting date	Not stated
Contact information	<p>Consorzio per le Valutazioni Biologiche e Farmacologiche  via Luigi Porta, 14  Pavia 27100 Italy  deep.2@deep-project.net</p>
Notes	

**IRCT2015101218603N2**

Trial name or title	To assess compliance, efficacy and satisfaction with two different formulation of deferasirox in people with transfusion-dependent beta-thalassaemia
Methods	RCT; parallel group
Participants	Inclusion criteria: signing informed consent; male or female aged $\geq 2$ years at screening; people with transfusion-dependent thalassaemia major; regular transfusion indicated by a blood requirement $\geq 8$ blood transfusions per year at screening Exclusion criteria: people with mean levels of ALT above 5-fold the ULN; people with serum creatinine above ULN; significant proteinuria as indicated by a urinary protein/creatinine ratio $> 0.6$ (mg/mg); creatinine clearance $\leq 60$ mL/min; chronic hepatitis B infection; active hepatitis C infection; pregnancy or breastfeeding; non-transfusion dependent thalassaemia
Interventions	DFX (new formulation Jadenu <sup>TM</sup> ), DFX (Exjade <sup>®</sup> )
Outcomes	Participants compliance and satisfaction; 3 months after drug consumption; designed questionnaire to assess participant compliance and satisfaction; ferritin serum amount; safety; possible GI side effects, including diarrhoea, and dermatologic symptoms
Starting date	22 December 2015
Contact information	Vice chancellor of research, Shiaz Univeisity of Medical Sciences COUNTRY: Iran SETTING: multicentre (outpatient) Dr. Sezaneh Haghpanah INSTITUTION: Hematology Research Center, Nemazee Hospital, Shiraz, Iran EMAIL: haghpanah@sums.ac.ir ADDRESS: Dr Sezaneh Haghpan Professor of community medicine Hematology Research Center, Nemazee Hospital, Zand Street, Shiraz, Ira
Notes	

**Madderom 2016**

Trial name or title	A randomised controlled trial studying the effectiveness of group medical appointments on self-efficacy and adherence in sickle cell disease (TEAM study): study protocol
Methods	RCT; parallel group
Participants	Inclusion criteria: individuals with homozygous or compound heterozygous SCD Exclusion criteria: individuals with a first visit to the outpatient clinic, patients who cannot communicate adequately due to language difficulties and/or hearing problems or patients who have behavioral problems which will limit group functioning
Interventions	Group Medical Appointment, Individual Medical Appointment (IMA; care-as-usual)

Outcomes	Primary and secondary endpoints will be measured at baseline (start of the study), after 1.5 years (after two GMA visits) and after 3 years (after four GMA visits), in both groups. Assessments are performed at the hospital, directly before the outpatient visit and in presence of a psychologist. Primary endpoint: 1. Self-efficacy as measured by the validated Sickie Cell Self- Efficacy Scale; Secondary endpoints; 2. Adherence to prescribed treatment by (paediatric) hematologist; 3. QoL as measured with the validated Pediatric Quality of Life Inventory for children and SF-36 for adults. 4. Emergency visits and hospital admissions for SCD related symptoms and complications. 5. Satisfaction with treating physician and nurse (by visual analogue scale: score 1 - 10); 6. Measurement of costs and effects in the GMA and IMA group by an economic analysis according to Dutch guidelines and with respect to an increase in self- efficacy
Starting date	The trial opened to recruitment in January 2013 for the children and in September 2015 for the adults and is still ongoing
Contact information	Marjon H. Cnossen INSTITUTION: Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital EMAIL: m.cnossen@erasmusmc.nl ADDRESS: Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Wytemaweg 80, PO Box 2060, 3000 CB Rotterdam, The NetherlandsAdditional data
Notes	Trial registration: NTR4750 (NL42182.000.12)

**NCT02173951**

Trial name or title	An algorithm to start iron chelation in minimally transfused young beta-thalassaemia major patients
Methods	RCT; parallel group
Participants	Inclusion criteria: young individuals with $\beta$ -thalassaemia major (diagnosed by HPLC, CBC) who started transfusion therapy who received 5 - 7 transfusions or less, aged more than 6 months. Pre-transfusional Hb should be $>9$ g/dL. Serum ferritin should be $\leq 500$ ng/mL, transferrin saturation $\leq 50\%$ Exclusion criteria: 1. individuals with $\beta$ -thalassaemia intermedia, those with other transfusion-dependent anemias (myelodysplasia, other chronic haemolytic anemias, pure red cell aplasia, aplastic anaemia); 2. Individuals with levels of ALT $> 5$ the ULN, serum creatinine $> ULN$ on 2 measurements; 3. Individuals with history of agranulocytosis (ANC $< 0.5 \times 10^9/L$ ). 4. Non-complaint individuals acknowledged by reviewing the patient's records
Interventions	DFP, placebo
Outcomes	Primary outcome measures: determine the time and number of transfusion units as well as amount of infused iron that will lead to appearance of LPI $> 0.2$ or TSAT $> 50\%$ , serum ferritin $\geq 500$ ng/mL in the studied thalassaemic patients which warrant start of iron chelation Time frame: 12 months To determine the time as well as amount of transfused iron (calculated in mg iron/kg) at which there is LPI appearance of $> 0.2$ as well as TSAT reaching $70\%$ , a serum ferritin $\geq 500$ in order to start iron chelation therapy

**NCT02173951** (Continued)

	<p>Secondary outcome measures:  Evaluation of safety of early use of iron chelation therapy in terms of drug related AEs or SAEs  Time frame: 12 months  To determine the tolerability and safety of early low dose DFP 50mg/kg and effectiveness to postpone or prevent SF from reaching 1000 ng/mL or LPI &gt; 0.6 or TSAT &gt; 70% in comparison to participants not starting chelation therapy</p>
Starting date	July 2014
Contact information	<p>Amira AM Adly,  INSTITUTION: Pediatric Hematology clinic, Ain Shams University Cairo, Egypt  EMAIL: amiradiabetes@yahoo.com</p>
Notes	

**NCT02435212**

Trial name or title	Study to evaluate treatment compliance, efficacy and safety of an improved deferasirox formulation (granules) in paediatric patients (2 - < 18 years old) with iron overload
Methods	RCT; parallel group
Participants	<p>Inclusion criteria: written informed consent/assent before any study-specific procedures. Consent will be obtained from parent(s) or legal guardians. Investigators will also obtain assent of patients according to local guidelines. Male and female children and adolescents aged <math>\geq 2</math> and &lt; 18 years. Any transfusion-dependent anaemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of approximately 20 PRBC units and a treatment goal to reduce iron burden (300 mL PRBC = 1 unit in adults whereas 4 mL/kg PRBC is considered 1 unit for children). Serum ferritin &gt; 1000 ng/mL, measured at screening visit 1 and screening visit 2 (the mean value will be used for eligibility criteria)</p> <p>Exclusion criteria: creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine (using the Schwartz formula) at screening visit 1 and screening visit 2 and the mean value will be used for eligibility criteria. Serum creatinine &gt; 1.5 x ULN at screening measured at screening visit 1 and screening visit 2 (the mean value will be used for eligibility criteria). ALT and/or AST &gt; 3.0 x ULN (Criterion no longer applicable, removed as part of amendment 1); prior iron chelation therapy. Liver disease with severity of Child-Pugh class B or C. Significant proteinuria as indicated by a urinary protein/creatinine ratio &gt; 0.5 mg/mg in a non-first void urine sample at screening visit 1 or screening visit 2. Those with significant impaired GI function or GI disease that may significantly alter the absorption of oral DFX (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome or small bowel resection)</p>
Interventions	DFX granule formulation, DFX DT formulation
Outcomes	<p>Primary outcome measures: compliance  Change in SF in iron chelation therapy-naïve participants.</p> <p>Secondary outcome measures: domain scores of treatment satisfaction and palatability over time  Overall safety, as measured by frequency and severity of adverse. This includes active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal haemorrhage)</p>

	<p>, and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations will be assessed.</p> <p>Rate of dosing instructions deviations ('Compliance', using a questionnaire) .</p> <p>Pre-dose DFX concentrations in all patients.</p> <p>Pre-dose PK data from all patients will be analysed to support the assessment of compliance.</p> <p>Post-dose DFX concentrations between 2 and 4 hours post-dose</p> <p>Change in SF in iron chelation therapy naive and pre-treated participants</p> <p>PK/PD relationship to explore exposure-response relationships for measures of safety and effectiveness: serum creatinine change from baseline, notable serum creatinine values, serum creatinine clearance change from baseline and notable serum creatinine clearance categories, SF change from baseline, in relationship to derived PK parameters for pre- and post-dose DFX concentrations.</p> <p>Assess additional safety, as measured by frequency and severity of adverse for granules during extension phase includes active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal haemorrhage), and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed</p>
Starting date	21 October 2015
Contact information	<p>Principal Investigator: Janet L. Kwiatkowski;</p> <p>INSTITUTION: Children's Hospital of Philadelphia Onc. Dept;</p> <p>EMAILContact: John Hammond 267-426-5602 hammondjh@email.chop.edu</p> <p>ADDRESS: Children's Hospital of Philadelphia, Oncology Dept, Philadelphia, Pennsylvania, USA, 19104-4399</p>
Notes	March 30, 2023 (Final data collection date for primary outcome measure)

AEs: adverse events  
 ALT: alanine transaminase  
 ANC: absolute neutrophil count  
 AST: aspartate transaminase  
 CBC: complete blood count  
 DFO: deferoxamine  
 DFP: deferiprone  
 DFX: deferasirox  
 DT: dispersible tablet  
 GI: gastrointestinal  
 HPLC: high-performance liquid chromatography  
 LIC: liver iron concentration  
 LPI: labile plasma iron  
 MRI: magnetic resonance imaging  
 PK/PD: pharmacokinetic/pharmacodynamic  
 QoL: quality of life  
 RBCs: red blood cells  
 RCT: randomised controlled trial  
 SAEs: serious adverse events  
 SF: serum ferritin

TSAT: transferrin saturation  
ULN: upper limit of normal  
WBC: white blood cell

## DATA AND ANALYSES

### Comparison 1. DFP versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adherence to iron chelation therapy (% ,SD)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 SAEs (from therapy, disease, non-adherence)	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
2.1 Agranulocytosis	1		Risk Ratio (M-H, Random, 99% CI)	0.0 [0.0, 0.0]
3 All-cause mortality	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Iron overload: defined as proportion of participants with serum ferritin $\geq$ 800 ( $\mu\text{g/L}$ )	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Organ damage	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Liver damage	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Other AEs related to iron chelation	3		Risk Ratio (IV, Random, 99% CI)	Subtotals only
6.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	192	Risk Ratio (IV, Random, 99% CI)	3.94 [0.44, 35.50]
6.2 Risk of pain or swelling in joints	3	192	Risk Ratio (IV, Random, 99% CI)	3.38 [0.54, 21.31]
6.3 Risk of nausea/vomiting	2	132	Risk Ratio (IV, Random, 99% CI)	13.68 [0.99, 188.88]
6.4 Risk of increased liver transaminase	1	44	Risk Ratio (IV, Random, 99% CI)	1.10 [0.03, 38.47]
6.5 Local reactions at infusion site	1	88	Risk Ratio (IV, Random, 99% CI)	0.17 [0.00, 9.12]

### Comparison 2. DFX versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adherence to iron chelation therapy (% ,SD)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 SAEs	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Thalassaemia-related SAEs	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 SCD-related SAE - painful crisis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 SCD-related SAEs - other SCD-related SAEs	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality (thalassaemia)	2	240	Risk Ratio (IV, Random, 95% CI)	0.96 [0.06, 15.06]

4 Proportion of participants with iron overload (thalassaemia)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Iron overload defined by ferritin 1500 (µg/l) or higher (Thalassaemia)	1	60	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.63, 2.20]
4.2 Proportion with severe iron overload (LIC at least 15 mg/Fe/g dw)	1	172	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.20]
4.3 Myocardial T2* < 10ms	1	172	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.72, 1.70]
5 Other AEs related to iron chelation - (thalassaemia)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Total chelation-related AE	1	187	Risk Ratio (IV, Random, 95% CI)	1.15 [0.76, 1.73]
5.2 Gastrointestinal upset	1	60	Risk Ratio (IV, Random, 95% CI)	3.0 [0.66, 13.69]
5.3 Rash	2	247	Risk Ratio (IV, Random, 95% CI)	3.05 [0.98, 9.47]
5.4 Risk of increased blood creatinine	1	187	Risk Ratio (IV, Random, 95% CI)	3.79 [0.83, 17.38]
5.5 Risk of proteinuria	1	187	Risk Ratio (IV, Random, 95% CI)	2.21 [0.59, 8.29]
5.6 Risk of increased ALT	1	187	Risk Ratio (IV, Random, 95% CI)	5.69 [0.70, 46.33]
5.7 Risk of increased AST	1	187	Risk Ratio (IV, Random, 95% CI)	5.69 [0.70, 46.33]
5.8 Risk of diarrhoea	1	187	Risk Ratio (IV, Random, 95% CI)	5.69 [0.70, 46.33]
5.9 Risk of vomiting	1	187	Risk Ratio (IV, Random, 95% CI)	6.64 [0.35, 126.78]
6 Total AEs (thalassaemia)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Other AEs related to iron chelation (SCD)	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
7.1 Risk of increased ALT	1	195	Risk Ratio (M-H, Random, 99% CI)	5.29 [0.12, 232.98]
7.2 incidence of abdominal pain	1	195	Risk Ratio (M-H, Random, 99% CI)	1.91 [0.80, 4.58]
7.3 Risk of pain or swelling in joints	1	195	Risk Ratio (M-H, Random, 99% CI)	1.06 [0.41, 2.76]
7.4 Risk of diarrhoea	1	195	Risk Ratio (M-H, Random, 99% CI)	4.14 [0.90, 18.92]
7.5 Nausea/vomiting	1	195	Risk Ratio (M-H, Random, 99% CI)	1.63 [0.90, 2.94]

### Comparison 3. DFX film-coated tablet versus DFX dispersible tablet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adherence to iron chelation therapy	1	173	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.99, 1.22]
2 Incidence of SAEs	1	173	Risk Ratio (IV, Random, 95% CI)	1.22 [0.62, 2.37]
3 All-cause mortality	1	173	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 71.81]
4 Incidence of organ damage (renal event)	1	173	Risk Ratio (IV, Random, 95% CI)	1.25 [0.83, 1.91]
5 Other AEs related to iron chelation	1		Risk Ratio (IV, Random, 99% CI)	Subtotals only
5.1 Total chelation-related AEs	1	173	Risk Ratio (IV, Random, 99% CI)	0.75 [0.52, 1.08]
5.2 Risk of diarrhoea	1	173	Risk Ratio (IV, Random, 99% CI)	0.70 [0.29, 1.70]



5.3 Increased urine protein/ urine creatinine ratio	1	173	Risk Ratio (IV, Random, 99% CI)	1.65 [0.60, 4.54]
5.4 incidence of abdominal pain	1	173	Risk Ratio (IV, Random, 99% CI)	0.49 [0.16, 1.52]
5.5 Incidence of nausea	1	173	Risk Ratio (IV, Random, 99% CI)	0.72 [0.23, 2.23]
5.6 Incidence of vomiting	1	173	Risk Ratio (IV, Random, 99% CI)	0.28 [0.07, 1.15]

#### Comparison 4. DFP and DFO versus DFP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of SAEs	1	213	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.81]
2 All-cause mortality	2	237	Risk Ratio (IV, Random, 95% CI)	0.77 [0.18, 3.35]
3 Incidence of chelation therapy- related AEs	3		Risk Ratio (IV, Random, 99% CI)	Subtotals only
3.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	280	Risk Ratio (IV, Random, 99% CI)	1.15 [0.50, 2.62]
3.2 Risk of pain or swelling in joints	2	256	Risk Ratio (IV, Random, 99% CI)	0.76 [0.31, 1.91]
3.3 Risk of gastrointestinal disturbances	1	213	Risk Ratio (IV, Random, 99% CI)	0.45 [0.15, 1.37]
3.4 Risk of increased liver transaminase	2	256	Risk Ratio (IV, Random, 99% CI)	1.02 [0.52, 1.98]
3.5 Nausea/vomiting	1	43	Risk Ratio (IV, Random, 99% CI)	0.55 [0.13, 2.23]

#### Comparison 5. DFP and DFO versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other AEs related to iron chelation	4		Risk Ratio (IV, Random, 99% CI)	Subtotals only
1.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	169	Risk Ratio (IV, Random, 99% CI)	1.18 [0.09, 15.37]
1.2 Risk of pain or swelling in joints	3	135	Risk Ratio (IV, Random, 99% CI)	2.39 [0.18, 32.31]
1.3 Risk of increased liver transaminase	2	104	Risk Ratio (IV, Random, 99% CI)	3.46 [0.45, 26.62]
1.4 Nausea/vomiting	4	194	Risk Ratio (IV, Random, 99% CI)	3.81 [0.84, 17.36]
1.5 Local reactions at infusion site	2	90	Risk Ratio (IV, Random, 99% CI)	0.18 [0.01, 3.56]

## Comparison 6. DFP/DFX versus DFP/DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adherence to iron chelation therapy rates	1	96	Risk Ratio (IV, Random, 95% CI)	0.84 [0.72, 0.99]
2 Incidence of SAE	1	96	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.53]
3 All-cause mortality	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Organ damage (serum creatinine $\geq 33\%$ ) above baseline in 2 consecutive occasions)	1	96	Risk Ratio (M-H, Random, 99% CI)	3.0 [0.16, 56.04]
5 Other AEs related to iron chelation	1		Risk Ratio (IV, Random, 99% CI)	Subtotals only
5.1 one year (study end)	1	96	Risk Ratio (IV, Random, 99% CI)	1.08 [0.68, 1.71]
5.2 Risk of leukopenia, neutropenia and/or agranulocytosis	1	96	Risk Ratio (IV, Random, 99% CI)	1.67 [0.27, 10.14]
5.3 Risk of pain or swelling in joints	1	96	Risk Ratio (IV, Random, 99% CI)	0.89 [0.29, 2.77]
5.4 Gastrointestinal problems	1	96	Risk Ratio (IV, Random, 99% CI)	0.6 [0.18, 2.04]
5.5 ALT (increase $\geq 3$ folds)	1	96	Risk Ratio (IV, Random, 99% CI)	1.33 [0.20, 8.88]
5.6 Skin rash	1	96	Risk Ratio (IV, Random, 99% CI)	5.0 [0.10, 261.34]

## ADDITIONAL TABLES

Table 1. Adherence Measurement and Results Table

STUDY	HOW ADHERENCE MEASURED	RESULTS
<b>Aydinok 2007</b>	<ul style="list-style-type: none"> <li>• Drug accounting at each visit (by counting the returned empty blisters of DFP and used vials of DFO)</li> <li>• Trial-specific designed questionnaire completed by the participants or their legal representative/ guardian (or both) at quarterly intervals</li> </ul>	<ul style="list-style-type: none"> <li>• Compliance was generally excellent during the entire trial period</li> <li>• 1 participant in the DFP treatment arm who missed more than 1 chelation dose per week because of problems with swallowing</li> </ul>
<b>Badawy 2010</b>	<ul style="list-style-type: none"> <li>• Questionnaire on chelation therapy, reasons for non-compliance, side effects, life activities, transfusion regimen</li> </ul>	<ul style="list-style-type: none"> <li>• Group II and group I were more compliant to chelation therapy but difference was statistically non significant</li> <li>• Non-compliant participants (compliance less than 50%) showed increase in their SF levels in all studied groups</li> <li>• In non-compliant participants the reduction in SF levels was higher in group I and III than in group II but difference was statistically non significant</li> </ul>

**Table 1. Adherence Measurement and Results Table** (Continued)

<b>Bahnasawy 2017</b>	<ul style="list-style-type: none"> <li>• Clinical pharmacist analysed data to detect unnecessary drug therapy, need for additional drug therapy, ineffective drug product, dosage too low, adverse drug reaction, dosage too high, non-compliance</li> </ul>	<ul style="list-style-type: none"> <li>• All 24 participants in intervention group had non-adherence at baseline and 3 where non-adherent at end of trial</li> <li>• No data on control group</li> </ul>
<b>Calvaruso 2015</b>	<ul style="list-style-type: none"> <li>• Counting the number of DFP pills in each returned bag</li> <li>• Assessing the number of infusions of DFO registered on the electronic pump</li> </ul>	<ul style="list-style-type: none"> <li>• DFP compliance rate: 85%</li> <li>• DFO compliance rate: 76%</li> </ul>
<b>El Beshlawy 2008</b>	<ul style="list-style-type: none"> <li>• Counting the returned empty blisters of DFP</li> <li>• Counting used vials of DFO</li> </ul>	<ul style="list-style-type: none"> <li>• 4 participants with DFO-based regimen excluded from the trial due to lack of compliance</li> <li>• Compliance was otherwise excellent during the entire trial period</li> <li>• Majority of participants had no problems with the intake and swallowing of the DFP tablets</li> <li>• 80% of participants in the combination arm and 76% of participants in the DFO monotherapy arm complained about difficulties in the parenteral use of DFO or problems to insert a needle</li> </ul>
<b>Elalfy 2015</b>	<ul style="list-style-type: none"> <li>• Counting of returned tablets for the oral chelators</li> <li>• Counting vials for DFO</li> <li>• The percentage of actual dose that patient had taken in relation to the total prescribed dose was calculated</li> </ul>	<ul style="list-style-type: none"> <li>• DFP/DFX: 95%</li> <li>• DFP/DFO: 80%</li> </ul>
<b>Galanello 2006</b>	<ul style="list-style-type: none"> <li>• DFP assessed by pill counts, diary cards and an electronic cap that recorded the time and date of each opening of the tablet container</li> <li>• DFO assessed by diary cards, weekly physical examination of infusion sites, and by the Crono™ infusion pump that recorded the number of completed infusions</li> </ul>	<ul style="list-style-type: none"> <li>• DFP/DFO: DFO: 96.1 ± 5.0 (29 participants)</li> <li>• DFP compliance was not reported</li> <li>• DFO: 95.7 ± 5.7 (30 participants)</li> </ul>
<b>Hassan 2016</b>	<ul style="list-style-type: none"> <li>• Records of all trial medications that were dispensed and returned</li> <li>• Parents were instructed to contact the investigator if the participant were unable to take the trial drug as prescribed</li> </ul>	<ul style="list-style-type: none"> <li>• All participants compliant with prescribed doses</li> <li>• No discontinuation of drugs or dropout of follow-up occurred</li> </ul>
<b>Maggio 2009</b>	<ul style="list-style-type: none"> <li>• Counting the pills in each returned bag of DFP</li> <li>• Assessing the number of infusions of DFO registered on the electronic pump</li> </ul>	<ul style="list-style-type: none"> <li>• DFP-DFO group: DFP: 92.7% (SD ± 15.2%; range 37-100%); DFO: 70.6% (SD ± 24.1%; range 25-100%)</li> <li>• DFP alone participants: 93.6% (SD ± 9.7%; range 56-100%)</li> </ul>

**Table 1. Adherence Measurement and Results Table** (Continued)

<b>Mourad 2003</b>	<ul style="list-style-type: none"> <li>• Number of vials of DFX used</li> <li>• Number of tablets of DFO used</li> </ul>	<ul style="list-style-type: none"> <li>• DFO/DFX group: compliance was excellent (arbitrarily defined as taking &gt; 90% of the recommended doses) in 10 participants and good (75% to 90% of recommended doses) in 1 participant</li> <li>• DFX alone group: compliance was considered to be excellent in 11 patients and good in 3 participants</li> </ul>
<b>Olivieri 1997</b>	<ul style="list-style-type: none"> <li>• Per cent of doses administered: number of doses of the iron chelator taken, out of number prescribed</li> <li>• DFP measured with computerised bottles</li> <li>• DFO measured using ambulatory pumps</li> <li>• Measured for a minimum of 3 months</li> </ul>	<ul style="list-style-type: none"> <li>• DFP: 94.9% <math>\pm</math> 1.1%</li> <li>• DFO: 71.6% <math>\pm</math> 3.7%</li> </ul>
<b>Pennell 2006</b>	<ul style="list-style-type: none"> <li>• DFP: measured using the Medication Event Monitoring System device calculated as the percent of openings with an interval longer than 4 hours recorded, divided by number of doses prescribed</li> <li>• DFO: calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed</li> </ul>	<ul style="list-style-type: none"> <li>• DFP: 94% <math>\pm</math> 5.3%</li> <li>• DFO: 93% <math>\pm</math> 9.7%</li> </ul>
<b>Pennell 2014</b>	<ul style="list-style-type: none"> <li>• Not stated how adherence was measured</li> </ul>	<ul style="list-style-type: none"> <li>• DFX: 99.0% <math>\pm</math> 3.5%</li> <li>• DFO: 100.4% <math>\pm</math> 10.9%</li> </ul>
<b>Taher 2017</b>	<ul style="list-style-type: none"> <li>• Assessed by relative consumed tablet count</li> </ul>	<ul style="list-style-type: none"> <li>• DT: 85.3% (95% CI: 81.1, 89.5)</li> <li>• FCT: 92.9% (95% CI: 88.8, 97.0)</li> </ul>
<b>Tanner 2007</b>	<ul style="list-style-type: none"> <li>• DFO: calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed</li> <li>• DFP/placebo: pill counting at the bimonthly visits</li> </ul>	<ul style="list-style-type: none"> <li>• DFO/placebo: DFO: 91.4 <math>\pm</math> 2.7%; placebo: 89.8 <math>\pm</math> 7.2%;</li> <li>• DFO/DFP: DFO: 92.6 <math>\pm</math> 2.7%; DFP: 82.4 <math>\pm</math> 18.1%</li> </ul>
<b>Vichinsky 2007</b>	<ul style="list-style-type: none"> <li>• DFX: counting the number of tablets returned in bottles at each visit</li> <li>• DFO: counting the numbers of vials returned at each visit</li> </ul>	<ul style="list-style-type: none"> <li>• Ratios of the administered to intended doses of therapy were high (1.16 for DFX and 0.97 for DFO), indicating high adherence to the prescribed treatment regimens</li> </ul>

DFO: deferoxamine

DFP: deferiprone

DFX: deferasirox

DT: dispersible tablet

FCT: film-coated tablet

SD: standard deviation

SF: serum ferritin

## CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: searching; selection of trials; eligibility assessment; content expert, and review content development
- Patricia Fortin: searching; selection of trials; eligibility assessment; data extraction, risk of bias assessment, and review content development.
- Karen Madgwick: selection of trials; eligibility assessment; data extraction, risk of bias assessment, content expert.
- Sally Hopewell: methodological expert and review development.
- Marialena Trivella: statistical and methodological expert and review development
- Sheila Fisher: data extraction, risk of bias assessment, review content development.

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Karen Madgwick: none to declare.

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Marialena Trivella: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Sheila Fisher: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See [Fortin 2016](#).

### Confidence intervals

In most studies we were unable to report total adverse events due to participants having one or more of the listed adverse events. We therefore use the 99% CI to report estimates of effects in subgroups of adverse events.

### Assessment of reporting biases

We could not assess reporting bias as there were fewer than 10 trials for each comparison

### Subgroup analysis

Due to insufficient data we could not undertake subgroup analyses as planned in the protocol (see below). From the outset, we also reported separately on the SCD trial.

- 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 could not undertake sensitivity analyses due to a lack of data.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Chelation Therapy; \*Patient Compliance; Anemia, Sickle Cell [mortality; \*therapy]; Benzoates [therapeutic use]; Deferoxamine [therapeutic use]; Iron Chelating Agents [\*therapeutic use]; Iron Overload [etiology; \*prevention & control]; Pyridones [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Triazoles [therapeutic use]; beta-Thalassemia [mortality; \*prevention & control]

### **MeSH check words**

Adolescent; Adult; Child; Humans