Iron chelation therapy in transfused and non-transfused patients with chronic anaemias: thalassaemia and sickle-cell disease.

QUESTION(S) TO BE ADDRESSED:

1. In transfused patients with thalassaemia major, thalassaemia intermedia, or sickle cell disease:

a) What is the evidence for the clinical effectiveness of deferoxamine (DFO) in achieving control of iron levels and preventing the complications of iron overload compared to deferasirox (DFX), deferiprone (DFP) and the combination of DFO/DFP?

b) What is the evidence for the cost-effectiveness of deferoxamine in achieving control of iron levels and preventing the complications of iron overload compared to deferasirox, deferiprone and the combination of DFO/DFP?

2. In non-transfused patients with thalassaemia intermedia, what is the evidence for the clinical and cost-effectiveness of any chelation therapy compared with no chelation therapy in achieving control of iron levels and preventing the complications of iron overload?

SUMMARY:

Background

- Beta-thalassaemia and sickle cell disease (SCD) are recessively inherited anaemias caused by variants of the haemoglobin genes.
- For many patients with inherited anaemias, regular red blood cell transfusions represent life saving therapy. However, with each unit of transfused blood, 200 to 250 mg of iron is transferred to the patient. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over 5 to 10 years) to toxic levels that affect major organs such as the heart and liver.
- The conventional treatment for transfusion related iron overload is long-term chelation therapy. There are three iron chelating agents available in the UK; deferasirox (DFX) and deferiprone (DFP) which are administered orally and deferoxamine (DFO) which is administered via subcutaneous infusion.

Clinical Effectiveness

- We found three Cochrane reviews of the clinical effectiveness of DFO, DFP and DFX in people with transfusion-dependent thalassaemia and one Cochrane review of the clinical effectiveness of DFX in people with sickle cell disease (SCD). We also identified three RCTs; one compared DFP with DFO in patients with SCD, one compared oral DFX against subcutaneous DFO for myocardial iron removal in thalassaemia patients and one assessed the efficacy and safety of DFX in iron-overloaded non-transfusion dependent thalassaemia (NTDT) patients.
- In patients with transfusion-dependent thalassaemia, a meta-analysis (MA) of three trials showed a significant difference in levels of ferritin reduction between treatment arms in

favour of combination therapy (DFP + DFO) compared to DFO (ratio of geometric mean ferritin reduction levels 1.17 (95% CI 1.10 to 1.23)). Another meta-analysis of 2 trials showed that left ventricular ejection fraction (LVEF) was significantly reduced in the DFO group compared with the DFO + DFP group (mean difference 6.22% (95% CI 4.32 to 8.12)). There was no significant difference in the reduction of liver iron levels between any treatment arms.

- In transfusion-dependent SCD patients, results from 2 studies showed greater serum ferritin reduction with DFO compared to DFX; mean difference 440.69µg/l (95% CI 11.73 to 869.64µg/l).
- Pennell et al carried out a prospective, randomised comparison of DFX vs. subcutaneous DFO for myocardial iron removal in 197 thalassaemia major patients with myocardial siderosis (deposition of iron) and no signs of cardiac dysfunction. They found that DFX was not inferior to DFO. The between-arm ratio of the geometric means was 1.056 (95% CI 0.998 to 1.133).
- In patients with NTDT, one RCT reported that liver iron concentration (LIC) decreased significantly compared with placebo (least-squares mean (LSM) ± standard error of the mean (SEM), -2.33 ± 0.7 mg Fe/g dry weight, P =0.001, and -4.18 ± 0.69 mg Fe/g dw, P <0 .001) for the 5 and 10 mg/kg/day DFX groups respectively. Serum ferritin decreased significantly compared with placebo (by LSM -235 and -337 ng/mL for the DFX 5 and 10 mg/kg/day groups, respectively (P < 0.001)).

Cost-Effectiveness

- We found four cost-effectiveness studies based on the UK health service perspective.
- Karnon et al in 2008 reported a cost-utility of DFX vs. DFO using a one year time frame. The results suggest that for thalassaemia, DFX treatment is likely to be cost-effective compared to DFO. In some scenarios deferasirox represents an increased cost compared with DFO. At a QALY threshold of £20,000 the probability that DFX is more cost-effective than DFO is 85%.Consideration of the compliance issues associated with DFO will strengthen the case for the cost-effectiveness of DFX compared to DFO.
- McLeod et al conducted a cost-effectiveness analysis of DFX vs. DFO and DFP in patients with β-thalassaemia and sickle cell disease as part of an HTA review.
- The economic model suggested that DFX may be cost-effective (cost per quality-adjusted life-year less than £30,000 per year) for β-thalassaemia major patients or sickle cell disease patients compared with DFO. However this was dependent on the age of the patient and the use of balloon infusers to administer DFO. DFX was unlikely to be cost-effective compared with DFP.
- The cost-utility analysis carried out by Karnon et al in 2012 showed that, although DFX patients incurred greater drug acquisition costs, these costs were offset by the avoidance of infusion-related equipment costs. The overall result was that, compared with DFO, DFX dominated costs less and patients gain more QALYs.
- In the sensitivity analysis the incremental cost-effectiveness ratio (ICER) was most sensitive to the equipment costs associated with the administration of DFO. In the worst case scenario analysis of 25% of DFO patients receiving DFO via balloon pump (the most expensive method) dominance was lost but the ICER remained well under £20,000 per additional QALY gained.
- Secondary analysis of DFX compared to combination therapy (DFO+ DFX) for highly iron overloaded patients showed DFX to be slightly less cost-effective although mean ICER was still under £5,000.
- Bentley et al assessed the cost-effectiveness of DFP, compared with other treatments for chronic iron overload, in patients with β-thalassaemia and an average weight of 63kg. DFP

was dominant in all scenario analyses, and in the one-way and two-way sensitivity analyses.

- The probabilistic sensitivity analysis estimated that the likelihood of DFP being cost-effective at a willingness-to pay threshold of £20,000 per QALY gained was over 99% for the main analysis and all scenario analyses.

Safety

- In the trials, adverse events were observed in all treatment groups.
- Adverse events were significantly less likely with DFO than DFP in one trial, relative risk (RR) 0.45 (95% CI 0.24 to 0.84), and significantly less likely with DFO alone than DFO combined with DFP in two other trials, RR 0.33 (95% CI 0.13 to 0.84). Permanent treatment withdrawal due to adverse events was higher with DFP than with DFO. The most commonly reported adverse event with DFP was joint pain, this occurred more frequently than with DFO, RR 2.64 (95% CI 1.21 to 5.77). Other common adverse events included gastrointestinal disturbances as well as neutropenia and/or leucopenia. The most commonly reported adverse event with DFO was reaction at the injection site.
- Adverse events also occurred at a higher frequency in patients who received DFX than DFO in one trial; however there was no difference in serious adverse events. Patient satisfaction was significantly better with DFX, but rate of discontinuations was similar for both drugs.
- Regular monitoring of white cell counts has been recommended for DFP and monitoring of liver and renal function for DFX.

Activity and Cost

- The estimated annual costs of the three iron chelation agents licensed in the UK are; deferoxamine £1,994 to £9303, deferiprone £4,993 and deferasirox £7,665 to £20,000.

Equity

- We did not identify any specific equity issues.

1 Context

1.1 Introduction

For many patients with chronic anaemias, regular red blood cell transfusions represent life saving therapy. However, with each unit of transfused blood, 200–250 mg of iron is transferred to the patient. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over 5–10 years) to toxic levels that affect major organs such as the heart and liver[1, 2]. This condition, commonly known as iron overload or transfusional haemosiderosis, can cause organ damage and death[3]. Currently the conventional way to prevent/or treat this is by long-term chelation therapy.

The most common chronic anaemic conditions that require frequent blood transfusions are beta-thalassaemia (β-thalassaemia) and sickle cell disease (SCD). β-thalassaemia and SCD are recessively inherited anaemias caused by variants of the haemoglobin genes.

Thalassaemia is the name given to a group of inherited blood disorders that cause the body to make fewer healthy red blood cells and less haemoglobin. There are two basic groups of thalassaemia disorders: alpha-thalassaemia and β-thalassaemia. These conditions result in varying degrees of anaemia, which can range from insignificant to life threatening. The most severe forms are known as alpha- or β-thalassaemia major and the least severe forms as alpha- or β-thalassaemia minor. Both forms of thalassaemia minor do not usually require any specific treatment whilst alpha-thalassaemia major usually results in intrauterine death. Beta-thalassaemia major involves frequent blood transfusions (possibly twelve or more each year). In addition, thalassaemia intermedia is associated with significant iron overload due to either increased oral iron absorption or intermittent blood transfusions. Some people with thalassaemia intermedia require regular blood transfusions but in general this is fewer than seven episodes per year. [4]

Sickle cell disease (SCD) is a highly heterogeneous group of disorders in which the red blood cells contain haemoglobin S with little or no normal haemoglobin A and can sickle when they are short of oxygen. Patients with SCD do develop vaso-occlusion in which the sickled red blood cells block blood vessels in the body leading to ‘painful crisis’, acute chest syndrome and stroke [5, 6, 7].

Unlike people with β-thalassaemia major, who require regular blood transfusions throughout life from soon after birth, the majority of people with SCD require red cell transfusions only occasionally and intermittently. However a small but increasing number of people with SCD are on long term transfusions, most commonly for secondary stroke prevention, but also for primary stroke prevention, or for recurrent pulmonary complications in people who have not responded to standard treatment[8].

Iron overload may be prevented or treated with a chelating agent that produces soluble complexes with iron, which allows excretion of chelator-iron complexes from the body. There are three iron chelating agents available in the UK; deferasirox and deferiprone which are administered orally and deferoxamine which is administered via subcutaneous infusion[9]. Deferoxamine has the widest range of licensed indications (see table 1 below).

1.2 Existing national policies and guidance

We found no existing evidence-based national guidance on the use of iron chelating agents in people with thalassaemia or sickle cell disease.

2 Epidemiology

Thalassaemia is more prevalent amongst Southern European, Middle Eastern, and African populations. It is estimated to affect about 12 per 100,000 of the UK population, although the prevalence in some ethnic groups is substantially greater and the prevalence in any locality will be affected by the proportion of the population that are genetically linked to susceptible populations[2, 10].

In the UK, about 12,500 people have SCD. It is more common in people whose family origins are African, African-Caribbean, Asian or Mediterranean. It is rare in people of North European origin. On average, 1 in 2,400 babies born in England have SCD, but rates are much higher in some urban areas - about 1 in 300 in some places[11].

3 The intervention

Deferoxamine (DFO) is one of the most widely used iron chelators, it was the traditional treatment before the advent of oral chelators. It has few toxic effects and has a 1:1 stoichiometry for iron (i.e. one molecule of DFO binds one molecule of iron), making it an effective chelating agent. However this drug is not orally active and has to be administered by subcutaneous infusion over 8 to 12 hours, 3 to 7 times per week due to its short half-life. This is inconvenient and often intolerable particularly in this relatively young group of patients, leading to poor compliance (up to one third of patients who have access to treatment do not adhere to it) [12].

Deferiprone, an oral iron chelator, is also available in the UK but is only licensed as a second-line treatment in patients for whom DFO is contraindicated or in those who experience serious toxicity with DFO. It has a lower affinity for iron than DFO (3:1 stoichiometry for iron). It is recommended to be taken three times daily[12, 13].

Deferasirox is a more recently licensed oral iron chelator, it is taken once daily[13].

Table 1: Licensed indications for iron chelating agents

Drug	Indications
Deferoxamine	Iron overload - acute iron poisoning; primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis; in patients in whom concomitant disorders (e.g. severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy; and for the diagnosis of iron storage disease and sideroblastic anaemia, auto-immune haemolytic anaemia and other chronic anaemias.
Deferiprone	Iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate.
Deferasirox	Chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Chronic iron overload due to blood transfusions when deferoxamine therapy is

	contraindicated or inadequate in the following patient groups: - in patients with beta thalassaemia major with iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) aged 2 to 5 years, - in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells) aged 2 years and older, - in patients with other anaemias aged 2 years and older. Also indicated for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older.

4 Findings

A literature search of studies of iron chelating agents in patients with chronic anaemia was carried out on the 9th of June 2014. We searched Medline, Embase, the Cochrane Library, Trip, DARE and NICE Evidence search – limited to English language. As there is a 2012 Cochrane review on deferasirox, we limited the search for clinical studies to 2012 onwards, but included economic studies from 2004 onwards. We also searched PubMed for the last three months for any recent e-publications ahead of print publication.

We found four Cochrane reviews; [9, 14, 15, 16] one assessed the clinical effectiveness of DFO in people with transfusion-dependent thalassaemia, one reviewed [14] the clinical effectiveness of DFP for iron chelation in people with thalassaemia, two other Cochrane reviews by Meerpohl et al studied the effectiveness of DFX in managing iron overload. One reviewed DFX in people with thalassaemia[15] and the other reviewed DFX in people with sickle cell disease[16]. We also identified three RCTs[17-19] one compared DFP with DFO in patients with SCD, one compared oral DFX against subcutaneous DFO for myocardial iron removal in thalassaemia patients and one assessed the efficacy and safety of DFX in iron-overloaded non-transfusion dependent thalassaemia (NTDT) patients.

We identified one systematic review of pharmacoeconomic studies of iron chelation therapy (ICT) in patients with β-thalassaemia and six other economic studies published subsequently [2, 20-25]. The systematic review excluded any studies that reported data for non-US populations and two of the six economic studies were based on Thailand and Iranian health systems respectively. We have therefore only reported on the cost-utility analyses based on the UK health service perspective[2, 22-24].

4.1 Evidence of effectiveness

Iron chelation therapy in transfused patients with chronic anaemias: thalassaemia and SCD

Deferoxamine (DFO)

The systematic (Cochrane) review by Fisher et al[9] determined the effectiveness (dose and method of administration) of deferoxamine in people with transfusion-dependent thalassaemia. The review also summarised data from trials on the clinical efficacy and safety of deferoxamine for thalassaemia and compared these with deferiprone and deferasirox.

A total of 22 trials involving 2187 participants (range 11 to 586 people) were included. Overall, few trials measured the same or long-term outcomes. See table 2 for a summary of the results.

The review suggests that DFO and the alternative oral iron chelators (DFP and DFX) produce a significant reduction in iron stores in transfusion-dependent, iron-overloaded people. They did not find any evidence to suggest that one treatment is more clinically efficacious than another. The authors concluded that in the absence of RCTs with long-term follow up, there is no compelling evidence to change the current recommendation that DFO should be first-line therapy for iron overload in people with thalassaemia major.

The review questions were supported by clear inclusion criteria for participants, intervention, outcomes and study design. The review process was performed by about six reviewers, reducing the possibility of reviewer error and bias.

Validity was assessed using an appropriate tool and trial quality was taken into consideration in the analysis. The authors discussed the limitations in terms of lack of generalisability to long-term outcomes.

The authors' conclusions appear to be reliable considering the limitations of the available evidence.

Deferiprone (DFP)

The systematic review by Fisher et al[14] summarised data from trials on the clinical efficacy and safety of DFP and compared the clinical efficacy and safety of DFP with DFO for thalassaemia.

A total of 17 trials involving 1061 participants (range 13 to 213 participants per trial) were included. Of these, 16 trials compared either DFP alone with DFO, or a combined therapy of DFP and DFO with either DFP alone or DFO alone; one compared different schedules of DFP. There was little consistency between outcomes and limited information to fully assess the risk of bias of most of the included trials.

The authors found that both DFP and DFO produce a significant reduction in iron stores in transfusion-dependent, iron-overloaded people. They did not find any evidence from RCTs to suggest that either has a greater reduction of clinically significant end organ damage or any conclusive or consistent evidence for the improved efficacy of combined DFP and DFO therapy over monotherapy from direct or indirect measures of liver iron. See table 2 for a summary of the results.
The authors concluded that in the absence of data from RCTs, there is no evidence to suggest the need for a change in current treatment recommendations; namely that DFP is indicated for treating iron overload in people with thalassaemia major when DFO is contraindicated or inadequate.

The review question was clear as were the inclusion criteria for participants, intervention, outcomes and study design. The review process was performed by at least two reviewers, reducing the possibility of reviewer error and bias.

Validity was assessed using an appropriate tool and trial quality was taken into consideration in the analysis. The authors discussed the limitations in terms of lack of generalisability to long-term outcomes.

The authors' conclusions appear to be reliable considering the limitations of the available evidence.

The RCT by Calvaruso et al[17] compared DFP with DFO in patients with SCD. This 5-year study which included 60 patients concluded that DFP is associated with efficacy and safety similar to that of DFO in patients with SCD. See table 2 for a summary of the results.

The authors addressed a clear question. The inclusion and exclusion criteria for participants, intervention, outcomes and study design were specified. A double-blinded design was not considered to be possible because of the subcutaneous administration of DFO, however all outcome assessments were coded by physicians blinded to the trial treatment. This study was probably too small to draw any firm conclusions particularly relating to safety.

Deferasirox (DFX)

Meerpohl et al[15] assessed the effectiveness and safety of oral DFX in people with thalassaemia and secondary iron overload. The review included four studies; two compared DFX with placebo and the other two compared DFX with DFO (standard treatment). See table 2 for summary of the results.

The authors concluded that DFX offers an important alternative line of treatment for people with thalassaemia and secondary iron overload. They noted that based on the available data, DFX does not seem to be superior to DFO at the usual recommended doses. Data on safety, particularly on rare toxicities and long-term safety are still limited. Therefore, the authors recommend that DFX should be offered as an alternative to all patients with thalassaemia who either show intolerance to DFO or poor compliance with DFO.
The research question was supported by clear inclusion criteria for participants, intervention, outcomes and study design. The review process was performed by at least two reviewers, reducing the possibility of reviewer error and bias.

Validity was assessed using an appropriate tool and trial quality was taken into consideration in the analysis. The authors discussed the limitations in terms of lack of generalisability to long-term outcomes.

The authors' conclusions appear to be reliable considering the limitations of the available evidence.

A separate review by Meerpohl et al[16]assessed the effectiveness and safety of oral DFX in people with SCD and secondary iron overload. They included two studies (involving 203 and 212 people) comparing the efficacy and safety of DFX and DFO after 12 months and 24 weeks, respectively. See table 2 for a summary of the results.

The authors concluded that DFX appears to be of similar efficacy to DFO at the usual recommended doses. However, they point out that only limited evidence is available which assesses the efficacy of outcomes important to patients.

The research question was supported by clear inclusion criteria for participants, intervention, outcomes and study design. The review process was performed by at least two reviewers, reducing the possibility of reviewer error and bias.

Validity was assessed using an appropriate tool and trial quality was taken into consideration in the analysis. The authors discussed the study limitations in terms of lack of generalisability of long-term outcomes.

The authors' conclusions appear to be reliable considering the limitations of the available evidence.

Pennell et al[18] carried out a prospective, randomised comparison of DFX vs. subcutaneous DFO for myocardial iron removal in 197 thalassaemia major patients with myocardial siderosis and no signs of cardiac dysfunction. They found that DFX was not inferior to DFO. The between-arm ratio of the geometric means was 1.056 with the 95% confidence intervals of 0.998 and 1.133). Mean left ventricular ejection fraction (LVEF) remained stable and within the normal range after 1 year of treatment with DFX (66.9– 66.3%) and DFO (66.4–66.4%). The change in mean LVEF after 1 year was not different between the two treatments (*P* = 0.54).

It should be noted that this study was sponsored by Novartis Pharmaceuticals, the manufacturers of DFX and DFO, although generic versions of DFO are now available.

Table 2: Summary of results from trials of patients with transfusion-dependent thalassaemia and/or sickle cell disease

Study	Patients	Intervention	Outcomes
Fisher et al. 2013 SR 22 trials at mixed sites Fisher et al. 2013 SR 17 trials at mixed sites	Transfusion-dependent thalassaemia N=2187 Transfusion-dependent thalassaemia N=1061	**Deferoxamine (DFO)** DFO vs. DFP (8). DFO + DFP vs. DFP (5), DFO vs. DFO + DFP (8), DFO vs. DFX (2), different routes of DFO routes (bolus vs. continuous infusion) (2) **Deferiprone (DFP)** DFP vs. DFO, DFP + DFO vs. DFP, DFP + DFO vs. DFO, different schedules of DFP (1)	**Primary Outcome:** Mortality *5 trials reported a total of 7 deaths; 3 in patients who received DFO alone, 2 in patients who received DFO + DFO. One in a patient who received DFP & another who received DFX alone. One trial reported 5 further deaths in patients who withdrew from randomised treatment (DFP ± DFO) & switched to DFO alone.* **Secondary Outcomes** ***Reduction in serum ferritin levels*** *– meta-analysis (MA) of 3 trials showed a significant difference between treatment arms 1.17 times in favour of combination therapy (DFP + DFO) compared with DFO; ratio of geometric means 1.17 (95%CI 1.10 to 1.23)* ***Reduction in liver iron*** *– No significant (NS) difference between any treatment arms* ***Reduction in cardiac iron*** *– MA of 2 trials showed left ventricular ejection fraction (LVEF) was significantly reduced in DFO group compared with DFO + DFP group mean difference (MD) 6.22% (95% CI 4.32 to 8.12)* ***Adverse effects*** *– AE with all treatment but less with DFO compared with DFP relative risk (RR) 0.45 (95%* CI *0.24 to 0.84) and significantly less likely with DFO alone than DFO + DFP, RR 0.33 (95%* CI *0.13 to 0.84).*
Calvaruso et al. 2014 Randomised open-label trial at 9 centres in Italy	SCD > 13 years old n=60	DFP vs. DFO	**Primary Outcome:** Change in serum ferritin levels at 5 years NS between treatment groups **Secondary Outcomes:** Safety and survival analysis There was NS difference in safety and survival analysis between the treatment groups
Meerpohl et al. 2012 SR 4 trials at mixed sites	Transfusion-dependent thalassaemia N=1061	**Deferasirox (DFX)** DFX vs. placebo, DFX vs. DFO	**2 studies - Dose finding, efficacy not focus of studies.** **Primary Outcome:** Mortality (2 studies) *NS difference between treatment arms* **Secondary Outcomes (2 studies)** *NS difference in measure of iron overload between treatment arms at recommended doses*
Meerpohl et al. 2014 SR 2 trials at mixed sites	Transfusion-dependent SCD N=415	**Deferasirox (DFX)** *DFX vs.DFO*	**Primary outcome** – Mortality (1 study) *At 24 weeks RR 1.26 (95% CI 0.05 to 30.41) in favour of DFO, however death is not thought to be related to study drug* **Secondary outcomes (2 studies)** ***Serum ferritin reduction*** *greater in DFO; MD of change 440.69µg/l (95% CI 11.73 to*

			869.64µg/l) ***Adverse events**: mean increase in creatinine 3.24 µmol/l higher in the DFX group.(95% CI 0.45 to 6.03)* *Differences in favour of DFO observed in diarrhoea and nausea; RR 3.09 (95% CI 1.53 to 6.26); and RR 2.06 (95% CI 1.11 to 3.80) respectively*
Pennell et al 2014 Multicenter, Randomized, Open-label Phase II Trial	10 – 65 years old with myocardial iron due to chronic blood transfusions	**Deferasirox (DFX)** DFX vs. DFO	**Primary outcome: ratio of geometric means of DFX over DFO** 1.056 (95% CI 0.998, 1.133) **Secondary outcomes: Changes in myocardial iron, LVEF, LIC and serum ferritin after 1 year** **Myocardial iron** DFX- *absolute change from baseline, −0.24 ± 0.7 mg Fe/g dw; 95% CI, −0.1, −0.4* DFO- *absolute change from baseline, −0.15 ± 0.5 mg Fe/g dw; 95% CI, −0.03, 0.3* **LVEF** DFX - 66.9% ± 5.6% at baseline to 66.3% ± 5.8% at end of study; DFO- 66.4% ± 5.2% to 66.4% ± 5.8% (p=0.54) **LIC** DFX- absolute change from baseline, −8.9 ± 11.4 mg Fe/g dw; (95% CI, −11.5, −6.4) DFO- *change from baseline, −12.7 ± 11.4 mg Fe/g dw; 95% CI, −15.3, −10.1* **Serum ferritin** DFX- *absolute change from baseline, −1044 [−5561-18 838] ng/mL* DFO- *change from baseline, −1277 [−7577-2810] ng/mL*

Table 3: Summary of results from trials of patients with non-transfusion-dependent thalassaemia

Study	Patients	Intervention	Comparator	Outcomes
Taher et al. 2012 THALASSA study (Phase II RCT) Multicentre	Non-transfusion dependent thalassaemia n= 166 (148 completed the study – 89.2%)	DFX 5mg or 10mg/kg/d	placebo	**Primary Outcome:** Change in liver iron concentration (LIC) from baseline at 52 weeks LIC decreased significantly compared with placebo (least-squares mean [LSM] ± standard error of the mean (SEM),-2.33 ± 0.7 mg Fe/g dry weight [dw], *P* =0.001, and -4.18 ± 0.69 mg Fe/g dw, *P* <0 .001) for the 5 and 10 mg/kg/d DFX groups, respectively **Secondary Outcomes:** Change in serum ferritin from baseline at 52 weeks Serum ferritin decreased significantly compared with placebo by LSM -235 and -337 ng/mL for the DFX 5 and 10 mg/kg/d groups, respectively (*P* < 0.001).

Iron chelation therapy in non-transfused patients with chronic anaemias: thalassaemia and SCD

We identified one RCT which assessed the efficacy and safety of DFX in iron-overloaded NTDT patients. This RCT carried out by Taher et al which included 166 patients concluded that DFX significantly reduces iron overload in NTDT patients with a frequency of overall adverse events similar to placebo. See table 3 for a summary of the results. It should be noted that this trial was sponsored by the pharmaceutical company, Novartis Pharma AG.

A clear question was addressed and the inclusion and exclusion criteria for participants, intervention, outcomes and study design were specified. DFX was not compared to standard treatment so its role in the treatment pathway cannot be determined by this study.

Trials in progress

NCT02041299: This study is currently recruiting participants. The trial is studying the efficacy and safety of Ferriprox® (deferiprone) for the treatment of transfusional iron overload in patients with sickle cell disease or other anaemias compared with deferoxamine. The estimated study completion date is March 2016.

4.2 Evidence of cost-effectiveness

Karnon et al[22] reported a cost-utility of DFX vs. DFO in relation to UK practice. The study used a one year time frame and also monitored direct costs of drugs (2007 prices), administration and treatment of adverse effects. Compliance was assumed to be equal. DFX was found to be less expensive and more effective than DFO in the reference thalassaemia patient, estimated to be 42kg. For a patient weighing 62kg, cost per QALY was £7,775 and at 72kg, £16,720 for DFX treatment against DFO. The results suggest that for thalassaemia, DFX treatment is likely to be cost-effective compared to DFO. At a QALY threshold of £20,000 the probability that DFX is more cost-effective than DFO is 85%.Consideration of the compliance issues associated with DFO will strengthen the case for the cost-effectiveness of DFX compared to DFO.

It should be noted that this study was sponsored by Novartis Pharmaceuticals, the manufacturers of deferasirox and deferoxamine, although generic versions of deferoxamine are now available.

McLeod et al[2] conducted a cost-effectiveness analysis of DFX vs. DFO and DFP in patients with β-thalassaemia and sickle cell disease as part of an HTA review. A one-year model was used given the lack of long term data on the effectiveness of DFX. In addition to costs of drugs and administration, costs of mode of administration of DFO by balloon infuser or traditional pump were also considered but costs of adverse effects were not.

Compared to DFO administered by traditional pump, DFX is cost-effective to approximately 6 years of age (ICER < £20,000 per QALY), over age 10 it is unlikely to be cost-effective (ICER >£30,000). If DFO is administered by the more expensive balloon infuser, treatment with DFX is the dominant therapy (cheaper and more effective) to approximately 14 years. Above age 14, DFO is cost-effective. In comparison to DFP, and assuming both treatments provide the same utility (valued equally by patients), DFX is not cost-effective at any age.

Karnon et al[23] carried out a cost-utility analysis of DFX in transfusion-dependent β-thalassaemia patients (at least 6 years old) with chronic iron overload from a UK health service perspective. The study evaluated the cost and outcomes over a lifetime horizon. The applied Markov model consisted of three core health states; alive without cardiac complications, alive with cardiac complications and death. Evidence for efficacy was based on a pivotal non-inferiority trial[26, 27] which showed that DFX was non-inferior to DFO and assumed no difference in treatment effects for similar levels of compliance. Acquisition costs for DFX and DFO (branded and generic respectively) were based on British National Formulary (BNF) prices and IMS™ data which showed 75% use of DFO in UK hospitals.

The analysis showed that, although DFX patients incurred greater drug acquisition costs, these costs were offset by the avoidance of infusion-related equipment costs. The overall result was that, compared with DFO, costs of DFX were less and patients gained more QALYs.

In the sensitivity analysis the incremental cost-effectiveness ratio (ICER) was most sensitive to the equipment costs associated with the administration of DFO. In the worst case scenario of 25% of DFO patients receiving DFO via a balloon pump (the most expensive method); the ICER remained well under £20,000 per additional QALY gained.

A secondary analysis carried out to evaluate high dose DFX versus DFO + DFX showed that DFX had higher costs due to higher dose of DFX and lower equipment costs (DFO frequency was reduced). However DFX was predicted to gain 2.5 additional QALYs leading to an ICER of £4,925. Assuming 50% usage of the balloon infusor and worse case scenarios for the other key parameter, the ICER increased to £25,173 per QALY gained.

This study had a clearly defined perspective and the source and basis of all costs and data were presented and tested in the sensitivity analyses. It is not clear, however, how or whether differences in side effects between the two treatments were taken into account.

It should be noted that this study was sponsored by Novartis Pharmaceuticals, the manufacturers of deferasirox and deferoxamine, although generic versions of deferoxamine are now available.

Bentley et al[24] assessed the cost-effectiveness of DFP, compared with other treatments for chronic iron overload, in patients with β-thalassaemia and an average weight of 63kg. A Markov model was developed to assess the cost-effectiveness of the treatments over five years, with a one-year cycle length. The study was undertaken from a UK NHS perspective.

Based on data from RCTs and observational studies, it was assumed that DFO and DFX had the same effects on cardiac mortality and morbidity, and DFP improved cardiac outcomes compared with DFO and DFX. All treatments were assumed to have comparable effects on serum ferritin concentration and liver iron concentration. The cost categories were drug acquisition, administration, laboratory tests, and the management of adverse events. The costs were from a range of UK sources.

In the main analysis, DFP was dominant, producing more QALYs for less cost than each of the other treatments. DFP cost £27,191 and produced 3.918 QALYs; DFO cost £72,442 and produced 3.006 QALYs; combination therapy cost £86,647 and produced 3.246 QALYs; and DFX cost £107,363 and produced 3.819 QALYs.

DFP was dominant in all scenario analyses, and in the one-way and two-way sensitivity analyses. The probabilistic sensitivity analysis estimated that the likelihood of DFP being cost-effective at a willingness-to pay threshold of £20,000 per QALY gained was over 99% for the main analysis and all scenario analyses.

The study was generally well reported and used appropriate methods. There were some issues with data availability and the time horizon was insufficient to assess the long-term cost-effectiveness. Whilst these limitations increase the uncertainty, the results were robust in a range of sensitivity analyses.

However it should be noted that the study was funded by ApoPharma Inc, a subsidiary of Apotex the manufacturer of DFP.

4.3 Safety

In the trials, adverse events were observed in all treatment groups. Occurrence of any adverse event was significantly less likely with DFO than with DFP in one trial, relative risk (RR) 0.45 (95% CI 0.24 to 0.84) and significantly less likely with DFO alone than with DFO combined with DFP in two other trials, RR 0.33 (95% CI 0.13 to 0.84). In particular, four studies reported permanent treatment withdrawal due to adverse events from DFP; only one of these reported permanent withdrawals associated with DFO[9]. The most commonly reported adverse event was joint pain; this occurred significantly more frequently in patients receiving DFP than DFO, RR 2.64 (95% CI 1.21 to 5.77). Other common adverse events included gastrointestinal disturbances as well as neutropenia or leucopenia, or both[14]. Eight trials reported adverse reactions at the infusion site with DFO, mainly pain and swelling[9].

In one trial, adverse events also occurred at a higher frequency in patients who received DFX compared with those on DFO[9]. Adverse events associated with DFX comprised increases in liver enzymes and renal impairment. The mean increase of creatinine was also significantly higher with DFX, mean difference 3.24 (95% CI 0.45 to 6.03)[16]. This is consistent with the summary of product characteristics information. Patient satisfaction was reported to be significantly better with DFX, but the rate of discontinuations was similar for both drugs[15].

Regular monitoring of white cell counts has been recommended for DFP and monitoring of liver and renal function for DFX[9, 14, 16].

4.4 Summary of section 4

We found three Cochrane reviews[9, 14, 15] of the clinical effectiveness of DFO, DFP and DFX in people with transfusion-dependent thalassaemia and one Cochrane review[16] of the clinical effectiveness of DFX in people with sickle cell disease (SCD). We also identified three RCTs[17-19] one compared DFP with DFO in patients with SCD, one compared oral DFX against subcutaneous DFO for myocardial iron removal in thalassaemia patients and one assessed the efficacy and safety of DFX in iron-overloaded non-transfusion dependent thalassaemia (NTDT) patients.

The majority of trials included patients with β thalassaemia major or thalassaemia. Most trials provided data on serum ferritin or liver iron concentration. There was a high degree of heterogeneity between trials in terms of trial design and outcome reporting such that meta-analysis could not be carried out on most of the results.

Deferoxamine and the oral iron chelators, DFP and DFX produce significant reductions in iron stores in transfusion-dependent, iron-overloaded people. There is no evidence from RCTs to suggest that any one of these has a greater effect on end organ damage. There is also no conclusive or consistent evidence for the improved efficacy of combined DFP and DFO therapy over monotherapy from direct or indirect measures of liver iron. However evidence from a meta-analysis of two trials of combination therapy with DFO and DFP showed a greater improvement in left ventricular ejection fraction than DFO used alone.

Although the three iron chelating agents appear to be of similar efficacy, there is evidence that adverse events are increased in patients treated with DFP compared with DFO and in patients treated with combined DFP and DFO compared with DFO alone. The short-term safety of DFX seems to be acceptable but follow up in the available studies was too short to assess long term side effects.

People treated with all chelators must be kept under close medical supervision and treatment with DFP or DFX requires regular monitoring of neutrophil counts or renal function respectively.

We found four cost-effectiveness studies based on the UK health service perspective.

Karnon et al in 2008 reported a cost-utility of DFX vs. DFO using a one year time frame. The results suggest that for thalassaemia, DFX treatment is likely to be cost-effective compared to DFO. In some scenarios deferasirox represents an increased cost compared with DFO. At a QALY threshold of £20,000 the probability that DFX is more cost-effective than DFO is 85%.Consideration of the compliance issues associated with DFO will strengthen the case for the cost-effectiveness of DFX compared to DFO.

McLeod et al conducted a cost-effectiveness analysis of DFX vs. DFO and DFP in patients with β-thalassaemia and sickle cell disease as part of an HTA review. The economic model suggested that DFX may be cost-effective (cost per quality-adjusted life-year less than £30,000 per year) for β-thalassaemia major patients or sickle cell disease patients compared with DFO. However this was dependent on the age of the patient and the use of balloon infusers to administer DFO. DFX was unlikely to be cost-effective compared with DFP.

The cost-utility analysis carried out by Karnon et al in 2012 showed that, although DFX patients incurred greater drug acquisition costs, these costs were offset by the avoidance of infusion-related equipment costs. The overall result was that, compared with DFO, DFX dominated costs less and patients gain more QALYs.

In the sensitivity analysis the incremental cost-effectiveness ratio (ICER) was most sensitive to the equipment costs associated with the administration of DFO. In the worst case scenario analysis of 25% of DFO patients receiving DFO via balloon pump (the most expensive method) dominance was lost but the ICER remained well under £20,000 per additional QALY gained.

Secondary analysis of DFX compared to combination therapy (DFO+ DFX) for highly iron overloaded patients showed DFX to be slightly less cost-effective although mean ICER was still under £5,000.

Bentley et al assessed the cost-effectiveness of DFP, compared with other treatments for chronic iron overload, in patients with β-thalassaemia and an average weight of 63kg. DFP was dominant in all scenario analyses, and in the one-way and two-way sensitivity analyses.

The probabilistic sensitivity analysis estimated that the likelihood of DFP being cost-effective at a willingness-to pay threshold of £20,000 per QALY gained was over 99% for the main analysis and all scenario analyses.

One study showed that DFX at starting doses of 5 and 10 mg/kg/day, with dose escalations up to 20 mg/kg/day in patients with higher levels of iron overload, significantly reduced iron overload in NTDT patients compared with placebo had a similar frequency of overall adverse effects.

We did not find any published analysis of the cost-effectiveness of iron chelation therapy in reducing iron overload in NTDT patients.

5 Cost and Activity

Drug	Dose	Approximate annual cost
Deferoxamine	20-50mg/kg daily	£1,994 - £9,303
Deferiprone	25mg/kg three times daily	£4,993
Deferasirox	10-30mg/kg once daily	£7,665 - £20,000

Prices are drug costs from the BNF September 2013 to March 2014. Costs are approximate and are based on an average body weight of 54kg, which has been suggested at the mean weight for patients needing iron chelation. Doses are shown for general comparison and do not imply therapeutic equivalence.

6 Equity issues

We did not identify any specific equity issues.

7 Discussion and conclusions

In transfused patients with thalassaemia major, thalassaemia intermedia, or sickle cell anaemia:

What is the evidence for the clinical effectiveness of deferoxamine in achieving control of iron levels and preventing the complications of iron overload compared to deferasirox, deferiprone and the combination of DFO/DFP?

Deferoxamine and the oral iron chelators, DFP and DFX produce significant reductions in iron stores in transfusion-dependent, iron-overloaded people. There is no evidence from RCTs to suggest that any one of these has a greater benefit on end organ damage. There is also no conclusive or consistent evidence for the improved efficacy of combined DFP and DFO therapy over monotherapy from direct or indirect measures of liver iron.

However, there is evidence that adverse events are increased in patients treated with DFP compared with DFO and in patients treated with combined DFP and DFO compared with DFO alone. The short-term safety of DFX seems to be acceptable; however, follow up in the available studies was too short to assess long term side effects.

What is the evidence for the cost-effectiveness of deferoxamine in achieving control of iron levels and preventing the complications of iron overload compared to deferasirox, deferiprone and the combination of DFO/DFP?

We found four cost-effectiveness studies based on a UK health service perspective. Three of these suggest that DFX is likely to be cost-effective compared with DFO but not compared with DFP. One found DFP to be cost-effective compared with DFO and DFX

One secondary analysis of DFX compared to combination therapy (DFO+ DFX) for highly iron overloaded patients showed DFX to be slightly less cost-effective although mean ICER was still under £5,000.

Two of the three analyses were sponsored by Novartis pharmaceuticals and one was funded by ApoPharma, a subsidiary of Apotex, the manufacturer of DFP.

In non-transfused patients with thalassaemia intermedia, what is the evidence for the clinical and cost-effectiveness of any chelation therapy compared with no chelation therapy in achieving control of iron levels and preventing the complications of iron overload?

Evidence from one RCT showed that DFX significantly reduced iron overload in NTDT patients compared with placebo and had a similar frequency of overall adverse effects.

We did not find any published analysis of cost-effectiveness of iron chelation therapy in reducing iron overload in NTDT patients.

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9 Search Strategy

Databases searched: Medline, Embase, Cochrane, TRIP and NICE Evidence
PubMed for the last three months for any recent e-publications ahead of print publication.

Search date: 09 June 2014

Medline searches:
1. Deferoxamine/
2. (deferoxamine or deferoxamine or desferal).ti,ab.
3. 1 or 2
4. exp anemia, sickle cell/ or exp thalassemia/
5. Blood Transfusion/ and exp Anemia/
6. thalass?emia*.ti,ab.
7. (sickle cell adj3 an?emia*).ti,ab.
8. (transfusion* adj3 an?emia*).ti,ab.
9. an?emia*.ti.
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10
12. limit 11 to (english language and yr="2013 -Current")
13. limit 11 to ("economics (best balance of sensitivity and specificity)" or "costs (best balance of sensitivity and specificity)")
14. limit 13 to (english language and yr="2004 -Current")

1. exp Iron Chelating Agents/
2. Deferoxamine/
3. (iron chelat* or deferoxamine or desferal or deferoxamine or deferasirox or exjade or deferiprone or ferriprox*).ti,ab.
4. (chelat* adj3 (therap* or treatment* or agent? or drug?)).ti,ab.
5. 1 or 2 or 3 or 4
6. beta-Thalassemia/
7. beta thalass?emia*.ti,ab.
8. b? thalass?emia*.ti,ab.
9. thalass?emia intermedia*.ti,ab.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. limit 11 to (english language and yr="2004 -Current")

13. limit 12 to "reviews (maximizes specificity)"
14. limit 12 to "therapy (best balance of sensitivity and specificity)"
15. limit 12 to ("economics (best balance of sensitivity and specificity)" or "costs (best balance of sensitivity and specificity)")

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Systematic review, meta-analysis, primary clinical study (any type) Economic study (any type). Abstracts were excluded where no clinical outcomes reported, or where the paper was a non-systematic literature review, editorial, letter, laboratory or animal study. Studies published as abstract only (e.g. conference poster) were excluded.
Patients	Transfused patients with: a) thalassaemia major, thalassaemia intermedia b) sickle cell anaemia Non transfused patients with Thalassaemia intermedia
Intervention	Deferoxamine
Comparators	Deferasirox Deferiprone monotherapy Combination therapy with deferiprone and deferoxamine No chelation therapy
Outcome	Mortality, prevention of liver iron overload, prevention of cardiac iron overload, treatment of cardiac iron overload, prevention of endocrinopathies: a) hypogonadism b) growth retardation or failure c) diabetes d) hypoparathyroidism • complications from chelation medication • complications relating to iron overload Cost-effectiveness
Language	English only