NHS England Evidence Review:

Deferiprone and Deferasirox combination therapy for patients with chronic inherited anaemias who develop iron overload

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of deferiprone (DFP) and deferasirox (DFX) combination therapy for the treatment of iron overload in patients with chronic inherited anaemias.

Inherited anaemia is an umbrella term covering a number of haemoglobinopathies and other red cell disorders passed down in families. They include sickle cell disease, thalassaemia and other rare anaemias including Diamond Blackfan anaemia, sideroblastic anaemia, pyruvate kinase deficiency, G6PD deficiency and rare red cell membrane disorders, congenital dyserythropoietic anaemias and enzymopathies. Blood transfusion is a common treatment for these inherited anaemias and can result in iron, a key component of haemoglobin, accumulating. Iron overload can cause damage to different organs in the body, resulting in poor growth, failure of puberty, the development of diabetes and other endocrine disorders, hepatic and cardiac complications.

Chelation therapy can be used to facilitate excretion of excess iron from the body. There are a number of standard chelation therapy regimes. The four current standard iron chelation drug treatment regimens are desferrioxamine[1] (DFO), DFP or DFX monotherapy or combination therapy with DFO/DFP. The combination of DFP/DFX is not currently a standard therapy. DFP and DFX are both taken orally and DFO is administered parenterally. All can be administered at any stage of the treatment pathway. Patients can be transfused or non-transfused.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from combination therapy with DFP/DFX more than others, the criteria used by the included studies to define patients eligible for combination therapy with DFP/DFX and the dose of DFP/DFX used.

Combination therapy with DFO/DFX is considered in a separate evidence review.

[1] Also known as Deferoxamine

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of deferiprone (DFP) and deferasirox (DFX) combination therapy for the treatment of iron overload in patients with chronic inherited anaemias. The searches for evidence published since January 2011 were conducted on 1 July 2021 and identified 799 potential references. These were screened using their titles and abstracts and 18 full text papers potentially relating to the combination of DFP/DFX were obtained and assessed for relevance.

Three papers were identified for inclusion, one randomised controlled trial (RCT) (Elalfy et al 2015) and two prospective cohort studies (Gomber et al 2016, Jhinger et al 2018). The RCT compared the combination of DFP/DFX (n=48) to the combination of desferrioxamine[2] (DFO) and DFP (n=48) in children with beta thalassaemia with 12 months follow-up. One prospective cohort study compared the combination of DFP/DFX (n=15) to monotherapy with either DFP (n=17) or DFX (n=17) in children with beta thalassaemia with 12 months follow-up. In the second prospective cohort study, children with beta thalassaemia received the combination of DFP/DFX (n=21) or monotherapy with either DFP (n=10) or DFX (n=9) with 15 months follow-up. No studies were identified comparing the combination of DFP/DFX to DFO monotherapy or to no chelation therapy. The RCT was conducted at two centres in Egypt and Oman. The prospective cohort studies were conducted at single centres in India[3].

In terms of clinical effectiveness:

- **Quality of life (critical outcome).** One RCT provided moderate certainty evidence of no statistically significant difference in quality of life between DFP/DFX and DFO/DFP combination therapies at 12 months. The improvement in quality of life from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP.
- **Progression of iron overload (critical outcome).**
  - One RCT provided high certainty evidence of no statistically significant difference in improvement in **serum ferritin** at 12 months between DFP/DFX and DFO/DFP combination therapies. The improvement in serum ferritin from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of a statistically significantly greater improvement from baseline to 12 months in serum ferritin level for combination therapy with DFP/DFX compared to monotherapy with either DFP or DFX. A second prospective cohort study provided very low certainty evidence of a statistically significant improvement in serum ferritin from baseline to 15 months for both combination therapy with DFP/DFX and monotherapy with either DFP or DFX. This study did not report statistical analysis comparing combination therapy and monotherapy.
  - One RCT provided high certainty evidence of no statistically significant difference in improvement in **liver iron** concentration (measured by MRI R2*) at 12 months between DFP/DFX and DFO/DFP combination therapies. The improvement in liver iron concentration from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of no statistically

[2] Also known as deferoxamine
[3] The precise location in India was only stated for one of the studies. However, the affiliations of the authors suggests that the studies were conducted at 2 different centres

significant difference in the change from baseline to six months in liver iron (measured by MRI T2*) for combination therapy with DFP/DFX or monotherapy with either DFP or DFX. A second prospective cohort study provided very low certainty evidence of no statistically significant difference in liver iron (measured by MRI T2*) from baseline to 15 months for combination therapy with DFP/DFX or monotherapy with either DFP or DFX. Neither of the two prospective cohort studies reported statistical analysis comparing combination therapy and monotherapy. The authors of both the prospective cohort studies categorised the liver iron overload reported at baseline and follow-up as mild[4].

- One RCT provided high certainty evidence of a statistically significantly greater improvement in **cardiac iron** (measured by MRI T2*) at 12 months for DFP/DFX and compared to DFO/DFP combination therapies. The improvement in cardiac iron from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of no statistically significant difference in the change from baseline to six months in heart iron (measured by MRI T2*) for combination therapy with DFP/DFX or monotherapy with either DFP or DFX. A second prospective cohort study provided very low certainty evidence of no statistically significant difference in cardiac iron (measured by MRI T2*) from baseline to 15 months for combination therapy with DFP/DFX or monotherapy with either DFP or DFX. Neither of the two prospective cohort studies reported statistical analysis comparing combination therapy and monotherapy. The authors of both the prospective cohort studies categorised the cardiac iron overload reported at baseline and follow-up as none[5].

- **Disease response (critical outcome).** One RCT provided moderate certainty evidence of no difference in change from baseline at 12 months for mean left ventricular ejection fraction (LVEF) between DFP/DFX and DFO/DFP combination therapies (no p value reported). The authors reported that mean LVEF remained stable and within the normal range after 12 months in both groups.

- **Adherence to treatment (important outcome).** One RCT provided high certainty evidence of a statistically significantly greater adherence to treatment at 12 months follow-up for combination therapy with DFP/DFX compared to combination therapy with DFO/DFP. In one prospective cohort study, two out of 21 children receiving combination therapy with DFP/DFX were excluded from the study due to poor compliance. No children receiving DFP or DFX monotherapy were reported to be non-compliant (very low certainty). This study did not report statistical analysis comparing combination therapy and monotherapy.

- **Mortality (important outcome).** No deaths were reported at 12 months follow-up for any of the treatment groups in one RCT (moderate certainty) and one prospective cohort study (very low certainty).

- No evidence was identified for psychological outcomes (important outcome) and activities of daily living (important outcome).

In terms of safety:

- **Adverse effects.** One RCT reported moderate certainty evidence of one serious adverse event each for DFP/DFX and DFO/DFP combination therapies. The serious adverse event for DFP/DFX was acute cholecystitis. It is not stated if this was

[4] Liver iron overload was graded as none >6.3ms; mild 6.3 to 2.7ms; moderate 2.7 to 1.4ms; severe <1.4ms
[5] Heart iron overload was graded as none >20ms; mild 12-20ms; moderate 8-12ms; severe <8ms

considered drug-related. The serious adverse event for DFO/DFP was appendicitis which was not considered to be drug-related. The number of drug-related adverse events was 58% and 54% and the number of non-drug-related adverse events was 35% and 38% for DFP/DFX and DFO/DFP respectively. The drug-related adverse events were described as mostly of mild to moderate severity with the most common drug-related adverse events being neutropenia, arthralgia and gastrointestinal problems. The most commonly reported non-drug-related adverse event was infection. One prospective cohort study reported one adverse event (arthropathy of large joints) (7%) for combination therapy with DFP/DFX, 0 (0%) adverse events for DFP and 2 (12%) adverse events (mild abdominal pain) for monotherapy with DFX. A second prospective cohort study stated that the most common adverse events with DFP/DFX were transient proteinuria (53%), mild abdominal symptoms (16%) and mild neutropenia (16%) and that the most common adverse events with DFX monotherapy were transient proteinuria (67%), abdominal pain (50%) and rash (50%). The authors reported that no "significant" adverse events were observed with DFP monotherapy. No statistical comparison between groups was reported by any of the studies.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from the combination of DFP/DFX than the wider population of interest.

Criteria used to define patients eligible to commence treatment with DFP/DFX[6]:

- The RCT included children aged 10 to 18 years with severe iron overload, defined as serum ferritin >2500 µg/L on maximum tolerated dose of a single iron chelator with upwards trend of serum ferritin over the 12 months prior to the study. Other inclusion criteria included patients with labile cellular iron >7 mg/g by MRI R2* and mean cardiac T2* <20 and >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, arrythmias). Adequacy of prior chelation was defined as taking >75% of the calculated dose/month on maximum tolerated dose with upward ferritin trend. For DFX this was reported to be 40 mg/kg/day, for DFP 100 mg/kg/day, for DFO >40-50 mg/kg.
- One prospective cohort study included children with serum ferritin >1500 ng/mL who were multi-transfused (not further defined). The second prospective cohort study included children with serum ferritin >4000 ng/mL.

Dose of DFP/DFX

- In the RCT, the dose was DFP 75 mg/kg/day divided into two oral doses combined with a single oral dose of DFX 30 mg/kg/day.
- In one prospective cohort study, the dose was DFP 75 mg/kg/day divided into three oral doses combined with DFX 30 mg/kg/day as a single oral dose.

[6] Abbreviations: kg: Kilogram; L: Litre; mg: Milligram; ml: Millilitres; ms: Milliseconds; ng: Nanograms; µg: Microgram

- In the second prospective cohort study, children received DFP and DFX on alternate weeks. The DFP dose was 75-100 mg/kg/day monotherapy divided into three to four oral doses. The DFX dose was 30-40 mg/kg/day monotherapy as a single oral dose.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

Limitations reducing the certainty in the RCT outcomes included lack of patient blinding in relation to self-reported outcomes and lack of statistical analysis for some outcomes. Limitations reducing certainty in both the prospective cohort studies included lack of detail about the study populations and whether the groups were similar at baseline, lack of identification of or adjustment for potentially confounding variables and, for some outcomes, the inclusion of a limited number of the patients and lack of statistical analysis.

Conclusion:

This evidence review includes one RCT and two prospective cohort studies. The populations of all three studies were children with beta thalassaemia.

One RCT provided high to moderate certainty evidence of no statistically significant difference between combination therapy with DFP/DFX or DFO/DFP at 12 months follow-up for the critical outcomes of quality of life, progression of iron overload (serum ferritin and liver iron) and disease response, with the quality of life and progression or iron overload outcomes showing a statistically significant improvement from baseline in both combination therapy groups. For one element of the critical outcome of progression of iron overload (cardiac iron) and the important outcome of adherence to treatment, the results favoured combination therapy with DFP/DFX (high to moderate certainty). No patients died in either of the treatment groups. The number of serious adverse events, drug-related adverse events and non-drug-related adverse events appeared similar between the combination therapy groups, however no statistical comparison was reported (moderate certainty).

One prospective cohort study provided very low certainty evidence favouring combination therapy with DFP/DFX compared to monotherapy with either DFP or DFX for the critical outcome of progression of iron overload (serum ferritin) with 12 months follow-up. There was no statistically significant difference between baseline and six months follow-up for either combination therapy or monotherapy for other elements of the critical outcome of progression of iron overload (liver iron or cardiac iron). This study did not report a statistical comparison between combination therapy and monotherapy for liver iron or cardiac iron. A second prospective cohort study reported an improvement in serum ferritin, but no difference for liver iron or cardiac iron, from baseline to 15 months for both combination therapy with DFP/DFX and monotherapy with either DFP or DFX (very low certainty). This study did not report a statistical comparison between combination therapy and monotherapy for these outcomes. The number of patients who were non-compliant with treatment was reported by one prospective cohort study, however the treatment groups were not compared statistically. One prospective cohort study reported that no patients died in any of the treatment groups. Adverse events were reported for both prospective cohort studies but were not compared between groups (all very low certainty).

The studies identified for this review therefore provide high to moderate certainty evidence that overall, for children with beta thalassaemia there may little difference in effectiveness and safety for combination therapy with DFP/DFX and combination therapy with DFO/DFP, with better adherence to treatment with DFP/DFX. There was limited, very low certainty evidence that combination therapy with DFP/DFX may have better outcomes than DFP or DFX monotherapy in terms of improvement in serum ferritin levels from baseline. The

limitations of the studies comparing combination therapy with DFP/DFX to monotherapy limit the conclusions that can be drawn for this comparison.

There was no evidence on cost effectiveness or on any subgroups of patients who might benefit more from treatment.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the clinical effectiveness of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

2. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the safety of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

3. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the cost effectiveness of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

4. From the evidence selected, are there any subgroups of patients that may benefit from the combination of DFP and DFX more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those patients diagnosed with iron overload in chronic inherited anaemias who are eligible to commence treatment with the combination of DFP and DFX?

6. From the evidence selected, what dose of DFP and DFX was used?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 1st July 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three papers were identified for inclusion, one RCT (Elalfy et al 2015) and two prospective cohort studies (Gomber et al 2016, Jhinger et al 2018). The RCT compared combination therapy with DFP/DFX to combination therapy with DFO/DFP in children with beta thalassaemia. In the prospective cohort studies, children with beta thalassaemia received combination therapy with DFP/DFX or monotherapy with either DFP or DFX. No studies were identified comparing combination therapy with DFP/DFX to DFO monotherapy or to no chelation therapy.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Elalfy et al 2015
 	
RCT
 	
2 treatment centres in Egypt and Oman
	96 children with beta thalassaemia and severe iron overload
	
	DFP/DFX: 48
	DFO/DFP: 48
	
	DFP/DFX
	Male: 66.6%
	Age years (mean ± SD): 14.05 ± 2.21
	
	DFO/DFP
	Male: 62.5%
	Age years (mean ± SD): 15.25 ± 2.31
	
	Groups were similar at baseline for age, sex, percentage of patients with excellent/good levels of compliance to chelation therapy, baseline clinical quality of life and haematological parameters, baseline iron burden, ALT and serum creatine, absolute neutrophil count and quality of life
	
	There was a statistically significant difference between groups in baseline haemoglobin (DFP/DFX 7.90 ± 0.38 Hb/g/dL vs DFO/DFP 8.11 ± 0.33 Hb/g/dL (p=0.004)
		Intervention
		DFP 75 mg/kg/day divided into 2 oral doses combined with a single oral dose of DFX 30 mg/kg/day
		
		Comparison
		DFO 40 mg/kg/day by subcutaneous infusion over 10 hours for 6 days per week combined with DFP 75 mg/kg/day divided into 2 oral doses for 7 days per week
		
		Concomitant treatments
		The transfusion regimen aimed to maintain the patients pretransfusion haemoglobin ≥8 g/dL. Patients received approximately 15 ml/kg packed red blood cells every 3-4 weeks
		
		Patients consumed a low iron diet (1-15mg of iron per day) throughout the study
			Critical outcomes
			• Quality of life (12 months) assessed using the SF-36[a]
			• Progression of iron overload (12 months)
			  • Serum ferritin levels µg/L
			  • Liver iron concentration by MRI R2* mg/g
			  • Cardiac MRI T2* ms
			• Disease response (12 months)
			  • LVEF
			
			Important outcomes
			• Adherence to treatment (12 months)
			• Mortality (12 months)
			• Safety (12 months)
			  • Severe adverse events
			  • Drug-related adverse events
			  • Non-drug-related adverse events

Study	Population	Intervention and comparison	Outcomes reported
	No subgroups reported		

Gomber et al 2016
 	
Prospective cohort study
 	
1 centre in India
	49 children with beta thalassaemia who had received multiple transfusions
	
	DFP/DFX: n=15
	DFP: n=17
	DFX: n=17
	
	Male: 61.2%
	Age years (mean; SD): 11.6; 6.21
	
	Groups reported to be similar at baseline for serum ferritin values. No other comparisons at baseline reported
	
	No subgroups reported
		Intervention
		DFP 75 mg/kg/day divided into 3 oral doses combined with DFX 30 mg/kg/day as a single oral dose
		
		Comparison
		DFP 75 mg/kg/day monotherapy divided into 3 oral doses
		
		DFX 30 mg/kg/day monotherapy as a single oral dose
		
		Concomitant treatments
		Patients received packed red blood cell transfusion every 3 weeks to maintain a pre-transfusion haemoglobin level of 9 to 9.5 g/dL
			Critical outcomes
			• Progression of iron overload
			  • Serum ferritin levels ng/mL (12 months)
			  • Liver MRI T2* ms (6 months)
			  • Heart MRI T2* ms (6 months)
			
			Important outcomes
			• Mortality (12 months)
			• Safety (12 months)
			  • Adverse events

Jhinger et al 2018
 	
Prospective cohort study
 	
1 centre in India
	40 children with beta thalassaemia
	
	DFP/DFX: n=21
	DFP: n=10
	DFX: n=9
	
	Male: 65.71%
	Age years (mean; SD): 9.71; 3.38
	
	No statistical comparison of the groups at baseline reported
	
	No subgroups reported
		Intervention
		DFP and DFX received on alternate weeks. DFP 75-100 mg/kg/day divided into 3-4 oral doses. DFX 30-40 mg/kg/day as a single oral dose
		
		Comparison
		DFP 75-100 mg/kg/day monotherapy divided into 3-4 oral doses
		
		DFX 30-40 mg/kg/day monotherapy as a single oral dose
		
		Concomitant treatments
		No information was provided about any concomitant treatments
			Critical outcomes
			• Progression of iron overload (15 months)
			  • Serum ferritin levels ng/mL
			  • Liver MRI T2* ms
			  • Cardiac MRI T2* ms
			
			Important outcomes
			• Adherence to treatment (15 months)
			• Safety (15 months)
			  • Severe adverse events
			  • Adverse events

Abbreviations ALT: Alanine transaminase; dL: Decilitre; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; g: Grams; Hb: Haemoglobin; kg: Kilogram; LVEF: Left ventricular ejection fraction; L: Litre; mg: Milligram; ml: Millilitres; ms: Milliseconds; MRI: Magnetic resonance imaging; ng: Nanograms; RCT: Randomised controlled trial; SD: Standard deviation; SF: short-form; µg: Microgram			
a The SF-36 is scored from 0 to 100 with higher scores indicating better quality of life			

5. Results

In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the clinical effectiveness and safety of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Quality of life **Certainty of evidence:** Moderate	This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF-36 which can provide information regarding improvement in symptoms. In total, one RCT provided evidence relating to quality of life at 12 months follow-up for children with beta thalassaemia and iron overload who received either combination therapy with DFP/DFX or combination therapy with DFO/DFP. Quality of life was assessed with the SF-36, which is scored from 0 to 100 with higher scores indicating better quality of life. **At 12 months:** • One RCT (Elalfy et al 2015) reported *no statistically significant difference* in quality of life between the two groups (DFP/DFX (n=48) vs DFO/DFP (n=48)) at 12 months (p=0.860). Mean (± SD) baseline scores were 63.38 ± 5.98 for DFP/DFX and 63.09 ± 5.77 for DFO/DFP. Data at 12 months only reported graphically. **(MODERATE)** The improvement in quality of life from baseline to 12 months was reported to be *statistically significant* for both the 48 children who received combination therapy with DFP/DFX (p=0.02) and the 48 children who received combination therapy with DFO/DFP (p=0.01). **One RCT provided moderate certainty evidence of no statistically significant difference in quality of life between the DFP/DFX and DFO/DFP combination therapy groups at 12 months. Quality of life improved statistically significantly at 12 months compared to baseline for both combination therapy with DFP/DFX and combination therapy with DFO/DFP.**
Progression of iron overload **Certainty of evidence:** High to very low	Preventing complications of disease and its progression is important to patients as it has the potential to maintain engagement in activities of daily living and prevent increasing dependence on others. Progression, or lack of progression, of iron deposition in tissues can provide critical information on treatment effectiveness. Iron burden in the liver reflects total body iron and iron in the heart is associated with increased mortality. Changes in iron stores can be determined sooner than overall survival outcome measures and therefore a useful survival outcome for trials with shorter follow-up periods. [Examples of measures include: liver iron stores as measured by R2MRI or T2* cardiac or liver iron assessment or persistently raised ferritin in those unable to undergo an MRI assessment. In total, one RCT and two prospective cohort studies provided evidence relating to progression of iron overload, with follow-up to 12 months or 15 months for children with beta thalassaemia and iron overload. The RCT compared combination therapy with DFP/DFX and combination therapy with DFO/DFP. The patients in the two prospective cohort studies received combination therapy with DFP/DFX or monotherapy with either DFP or DFX.

Outcome	Evidence statement
	The outcomes were serum ferritin, liver iron concentration measured by MRI R2* or T2*, and cardiac iron measured by MRI T2*. ***Serum ferritin*** **At 15 months:** • One prospective cohort study (Jhinger et al 2018) reported a *statistically significant improvement* from baseline to 15 months in serum ferritin levels (ng/mL) for 19 patients who received combination therapy with DFP/DFX (p=0.029). (Mean (SD) baseline: 4763.17 (1022); 15 months: 4023.56 (1084)). The patients who received monotherapy with DFP (n=10) or DFX (n=6) were also reported to have had *statistically significant improvements* from baseline to 15 months in serum ferritin levels (ng/mL) (p=0.011 and p=0.004 respectively). (DFP mean (SD) baseline: 5574.13 (1497); 15 months: 3388.88 (755); DFX mean (SD) baseline: 4394.5 (666); 15 months: 2988.83 (820)). **(VERY LOW)** **At 12 months:** • One RCT (Elalfy et al 2015) reported *no statistically significant difference* in improvement from baseline in serum ferritin (µg/L) between combination therapy with DFP/DFX (n=48) and combination therapy with DFO/DFP (n=48). (Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error): DFP/DFX 4212.85 ± 119.17 - 89.1 ± 15.38t; DFO/DFP 4383.98 ± 114.92 - 62.78 ± 14.84t; comparison of elevation and slope (d.f.=286), p=0.301 and 0.218 respectively)[7]. **(HIGH)** The improvement in serum ferritin (µg/L) at 12 months compared to six months and baseline was reported to be *statistically significant* for the 48 patients who received combination therapy with DFP/DFX (p=0.001) and the 48 children who received combination therapy with DFO/DFP (p=0.001). (DFP/DFX mean ± SD baseline: 4289.19 ± 866.21; 6 months: 3525.57 ± 952.31 (percent change -17.8%); 12 months: 3219.98 ± 882.25 (percent change -36.59%); DFO/DFP mean ± SD baseline: 4379.07 ± 895.00; 6 months: 4017.15 ± 861.33 (percent change -8.26%); 12 months: 3625.76 ± 869.13 (percent change -17.2%)). • One prospective cohort study (Gomber et al 2016) reported a *statistically significantly greater improvement* in serum ferritin (ng/mL) from baseline to 12 months for 15 patients who received combination therapy with DFP/DFX compared to 17 patients who received DFP monotherapy (p=0.035). (DFP/DFX mean (95%CI) baseline: 3696.5 (3079.6 to 4438.1); 6 months: 2977.1 (2384.5 to 3717.1); 12 months: 2572.1 (2138.9 to 3093.1); DFP mean (95%CI) baseline: 3140.5 (2617.5 to 3767.9); 6 months: 3010.9 (2548.5 to 3557.1); 12 months: 2910.0 (2220.7 to 3812.4)). **(VERY LOW)** • One prospective cohort study (Gomber et al 2016) reported a *statistically significantly greater improvement* in serum ferritin (ng/mL) from baseline to 12 months for 15 patients who received combination therapy with DFP/DFX compared to 17 patients who received DFX monotherapy (p=0.04). (DFP/DFX mean (95%CI) baseline: 3696.5 (3079.6 to 4438.1); 6 months: 2977.1 (2384.5 to 3717.1); 12 months: 2572.1 (2138.9 to 3093.1); DFX mean (95%CI) baseline: 3859.2 (3168.8 to 4700.0); 6 months: 3671.1 (3098.1 to 4350.1); 12 months: 3417.4 (2734.6 to 4270.7)). **(VERY LOW)**

[7] The linear regression analysis assessed the changes in each variable against time with calculation of the difference between the slopes (elevation and slope) of the studied groups. A significant difference between the slopes indicates that the therapy has produced significantly different effects between groups

Outcome	Evidence statement
	Liver iron **At 15 months:** • One prospective cohort study (Jhinger et al 2018) reported no *statistically significant difference* from baseline to 15 months in liver MRI T2* (ms) for 19 patients who received combination therapy with DFP/DFX (p=0.806). (Mean (SD) baseline: 5.62 (0.99); 15 months: 5.69 (0.87)). The patients who received monotherapy with DFP (n=10) or DFX (n=6) in the prospective cohort study were also reported to have had no *statistically significant difference* from baseline to 15 months in MRI T2* (ms) (p=0.260 and p=0.119 respectively). (DFP mean (SD) baseline: 6.19 (1.97); 15 months: 5.55 (0.44); DFX mean (SD) baseline: 5.89 (0.70); 15 months: 5.55 (0.65)). The liver iron overload levels reported for all patients at baseline and 15 months were categorised as mild by the authors.[8] **(VERY LOW)** **At 12 months:** • One RCT (Elalfy et al 2015) reported *no statistically significant difference* in decrease from baseline in liver iron concentration by MRI R2* (mg/g) between combination therapy with DFP/DFX (n=48) and combination therapy with DFO/DFP (n=48). (Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error): DFP/DFX 12.823 ± 0.286 – 0.196 ± 0.037t; DFO/DFP 12.732 ± 0.285 – 0.146 ± 0.037t; comparison of elevation and slope (d.f.=286), p=0.340 and 0.821 respectively). **(HIGH)** The improvement in liver iron concentration by MRI R2* (mg/g) at 12 months compared to six months and baseline was reported to be *statistically significant* for the 48 patients who received combination therapy with DFP/DFX (p=0.001) and the 48 children who received combination therapy with DFO/DFP (p=0.001). (DFP/DFX mean ± SD baseline: 12.52 ± 2.28; 6 months: 12.25 ± 1.9 (percent change -2.15%); 12 months: 10.17 ± 2.23 (percent change -18.77%); DFO/DFP mean ± SD baseline: 12.69 ± 2.23; 6 months: 11.95 ± 1.01 (percent change -5.8%); 12 months: 10.96 ± 2.95 (percent change -13.6%)). **At 6 months:** • One prospective cohort study (Gomber et al 2016) reported *no statistically significant difference* in change in liver MRI T2* (ms) from baseline to six months for children who received combination therapy with DFP/DFX (n=5), monotherapy with DFP (n=5) or monotherapy with DFX (n=5) (p not reported). (DFP/DFX mean (SD) baseline: 5.3 (0.26); 6 months: 5.5 (0.40); DFP mean (SD) baseline: 5.4 (0.20); 6 months: 5.6 (0.26); DFX mean (SD) baseline: 5.1 (0.52); 6 months: 5.4 (0.58)). The iron overload range at baseline and six months was categorised as mild[8] by the authors. **(VERY LOW)** ***Cardiac iron*** **At 15 months:** • One prospective cohort study (Jhinger et al 2018) reported *no statistically significant difference* from baseline to 15 months in cardiac MRI T2* (ms) for 19 patients who received combination therapy with DFP/DFX (p=0.51). (Mean (SD) baseline: 29.82 (3.28); 15 months: 28.03 (3.23)). The patients who received monotherapy with DFP (n=10) or DFX (n=6) in the prospective cohort study were also reported to have had *no statistically significant difference* from baseline to 15 months in MRI T2* (ms) (p=0.07 and p=0.901 respectively). (DFP mean (SD) baseline: 28.67 (4.56); 15 months: 30.72 (4.38); DFX mean (SD) baseline: 29.97 (4.01); 15 months: 29.75 (4.66)). The degree of cardiac iron overload reported for all patients

[8] Liver iron overload was graded as none >6.3ms; mild 6.3 to 2.7ms; moderate 2.7 to 1.4ms; severe <1.4ms

Outcome	Evidence statement
	at baseline and 15 months was categorised as none[9] by the authors. **(VERY LOW)** **At 12 months:** • One RCT (Elalfy et al 2015) reported a *statistically significant greater improvement* from baseline to 12 months for cardiac MRI T2* (ms) for combination therapy with DFP/DFX (n=48) compared to combination therapy with DFO/DFP (n=48). (Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error): DFP/DFX 16.656 ± 0.254 – 0.263 ± 0.033t; DFO/DFP 16.352 ± 0.210 – 0.125 ± 0.027t; comparison of elevation and slope (d.f.=286), p=0.357 and 0.001 respectively). **(HIGH)** There was a *statistically significant improvement* in cardiac MRI T2* (ms) at 12 months compared to six months and baseline for the 48 children who received combination therapy with DFP/DFX (p=0.001) and the 48 children who received combination therapy with DFO/DFP (p=0.002). (DFP/DFX geometric mean[10] ± SD baseline: 16.59 ± 1.85; 6 months: 18.36 ± 0.86 (percent change +10.67%); 12 months: 19.75 ± 2.65 (percent change +19.1%); DFO/DFP geometric mean ± SD baseline: 16.32 ± 1.82; 6 months: 17.17 ± 0.87 (percent change +5.21%); 12 months: 17.8 ± 1.89 (percent change +9.1%)). **At 6 months:** • One prospective cohort study (Gomber et al 2016) reported *no statistically significant difference* in change in heart MRI T2* (ms) from baseline to six months for children who received combination therapy with DFP/DFX (n=5) or monotherapy with DFP (n=5) or DFX (n=5) (p not reported). (DFP/DFX mean (SD) baseline: 29.5 (1.99); 6 months: 31.2 (2.57); DFP mean (SD) baseline: 33.3 (1.44); 6 months: 32.3 (1.66); DFX mean (SD) baseline: 32.0 (2.00); 6 months: 31.7 (2.65)). All patients at baseline and six months were categorised as not having heart iron overload by the authors[9]. **(VERY LOW)** **One RCT provided high certainty evidence of no statistically significant difference in improvement in serum ferritin between DFP/DFX and DFO/DFP combination therapies. The improvement in serum ferritin from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of a statistically significantly greater improvement from baseline to 12 months in serum ferritin level for combination therapy with DFP/DFX compared to monotherapy with either DFP or DFX. A second prospective cohort study provided very low certainty evidence of a statistically significant improvement in serum ferritin from baseline to 15 months for both combination therapy with DFP/ DFX and monotherapy with DFP or DFX. This study did not report statistical analysis comparing combination therapy and monotherapy.** **One RCT provided high certainty evidence of no statistically significant difference in improvement in liver iron concentration (measured by MRI R2*) between DFP/DFX and DFO/DFP combination therapies. The improvement in liver iron concentration from baseline to 12 months was statistically significant for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of no statistically significant difference in the change from baseline to six months in liver iron (measured by MRI T2*) for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. A second prospective cohort study provided very low certainty evidence of no statistically significant difference in liver iron (measured by MRI T2*) from baseline to 15 months**

[9] Heart iron overload was graded as none >20ms; mild 12-20ms; moderate 8-12ms; severe <8ms
[10] Geometric means calculated from the log-transformed T2* values

Outcome	Evidence statement
	for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. Neither of the prospective cohort studies reported statistical analysis comparing combination therapy and monotherapy. The authors of both the prospective cohort studies categorised the liver iron overload reported at baseline and follow-up as mild. **One RCT provided high certainty evidence of a statistically significantly greater improvement in cardiac iron (measured by MRI T2*) at 12 months for DFP/DFX compared to DFO/DFP combination therapies. Cardiac iron improved statistically significantly at 12 months compared to baseline for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. One prospective cohort study provided very low certainty evidence of no statistically significant difference in the improvement from baseline to six months in heart iron (measured by MRI T2*) for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. A second prospective cohort study provided very low certainty evidence of no statistically significant difference in cardiac iron (measured by MRI T2*) from baseline to 15 months for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. Neither of the prospective cohort studies reported statistical analysis comparing combination therapy and monotherapy. The authors of both the prospective cohort studies categorised the cardiac iron overload reported at baseline and follow-up as none.**
Disease response **Certainty of evidence:** Moderate	Disease response includes but is not limited to improvement in cardiac function, endocrine function (including pituitary, pancreatic, reproductive and bone health), reduction of hepatic iron stores or other validated measures of organ function). This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. In total, one RCT provided evidence relating to disease response at 12 months follow-up for children with beta thalassaemia and iron overload who received either combination therapy with DFP/DFX or combination therapy with DFO/DFP. Patients with suspected cardiac manifestations had chest radiography, electrocardiogram and echocardiography. Impaired left ventricular function was defined by a decrease in resting left ventricular ejection fraction (LVEF) either to a value <50%, or by >10% units between two consecutive measurements. **At 12 months:** • One RCT (Elalfy et al 2015) reported that there was *no difference* (p value not reported) in change from baseline in mean LVEF at 12 months between children who received combination therapy with DFP/DFX (n=48) and children who received combination therapy with DFO/DFP (n=48). Data values not reported. **(MODERATE)** • The RCT authors also reported that mean LVEF remained stable and within the normal range after 12 months for both combination therapy with DFP/DFX and combination therapy with DFO/DFP. No patients in either group had impaired ejection fraction or deterioration in cardiac function by echocardiography during follow-up. **One RCT provided moderate certainty evidence of no difference in change from baseline to 12 months for mean LVEF between DFP/DFX and DFO/DFP combination therapies.**
Important outcomes	
Adherence to treatment **Certainty of evidence:**	This is important to patients because it is vital to the function of iron chelating drugs that they are taken regularly as prescribed in order to gain the maximum effect, improve iron burden and prevent the complications of iron overload.

Outcome	Evidence statement
High to very low	In total, one RCT and one prospective cohort study provided evidence relating to adherence to treatment at 12 months and 15 months follow-up respectively for children with beta thalassaemia and iron overload. The RCT compared children who received either combination therapy with DFP/DFX or combination therapy with DFO/DFP. In the prospective cohort study patients received combined therapy with DFP/DFX or monotherapy with either DFP or DFX. In the RCT, patients' compliance with treatment was evaluated by counting the returned tablets for DFP and DFX and the vials for DFO. The percentage of actual dose that the patient had taken in relation to the total dose prescribed was calculated. It is not clear how compliance with treatment was assessed in the prospective cohort study. **At 15 months:** • One prospective cohort study (Jhinger et al 2018) reported that two of 21 children (9.5%) receiving combination therapy with DFP/DFX were non-compliant with treatment. No children receiving monotherapy with DFP or DFX were reported to be non-compliant with treatment. No statistical comparison between groups reported. **(VERY LOW)** **At 12 months:** • One RCT (Elalfy et al 2015) reported *statistically significantly better* treatment compliance for 48 children who received combination therapy with DFP/DFX (95%) compared to 48 children who received combination therapy with DFO/DFP (80%) (p<0.001). **(HIGH)** • The RCT authors also reported that a *statistically significantly higher* proportion of children receiving combination therapy with DFP/DFX reported always following their iron chelation therapy (p<0.001) and never thought about stopping iron chelation therapy (p<0.02), compared to children receiving combination therapy with DFO/DFP. No figures were reported for these comparisons. **(MODERATE)** **One RCT provided high certainty evidence of a statistically significantly greater adherence to treatment at 12 months follow-up for combination therapy with DFP/DFX compared to combination therapy with DFO/DFP. In one prospective cohort study, two patients receiving combination therapy with DFP/DFX were excluded from the study due to poor compliance. No DFP or DFX monotherapy patients were reported to be non-compliant. This study did not report statistical analysis comparing combination therapy and monotherapy.**
Psychological outcomes **Certainty of evidence:** Not applicable	These outcomes are important to patients because they can impact their mood, motivation and self-esteem which can have implications for treatment compliance. Positive healthcare outcomes rely upon patients' ability to comply with their rigorous treatment regimes. Delayed puberty due to poor iron control is the most common endocrine complication in thalassaemia. Often this can result in diminished self-esteem and body confidence as the secondary conditions causes illnesses that can deform, debilitate and disable them. Lack of concordance can be a ubiquitous threat to not only patients' physical health but compound their psychosocial well-being. **No evidence was identified for this outcome.**
Mortality **Certainty of evidence:** Moderate to very low	Mortality is usually the gold standard for assessing survival benefit of drug treatments. This outcome is important to patients because it considers whether the treatment reduces mortality although it does not reflect morbidity or patient experience. In total, one RCT and one prospective cohort study provided evidence relating to mortality at 12 months follow-up for children with beta thalassaemia and iron overload. The RCT compared children who received either combination therapy with DFP/DFX or combination therapy with DFO/DFP. In the

Outcome	Evidence statement
	prospective cohort study patients received combined therapy with DFP/DFX or monotherapy with either DFP or DFX. **At 12 months:** • One RCT (Elalfy et al 2015, n=96) reported that no patients died during the study in either treatment group. **(MODERATE)** • One prospective cohort study (Gomber et al 2016, n=49) reported that no patients died during the study in any treatment groups. **(VERY LOW)** **No deaths were reported at 12 months follow-up for any of the treatment groups in one RCT (moderate certainty) and one prospective cohort study (very low certainty).**
Activities of daily living (ADL) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home and recreational settings. They encompass patients' individual rehabilitation goals and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Moderate to very low	Adverse events are important to patients because they will impact on their treatment choices, adherence, recovery and could have long term sequelae if they are irreversible. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. [Serious adverse events include agranulocytosis, renal impairment, heart failure, and severe gastrointestinal side effects (e.g. perforated gastric ulcer). Common adverse effects include gastrointestinal disturbances (such as dyspepsia, gastrointestinal pain, nausea, vomiting, diarrhoea, and constipation), somatic complaints, physical symptoms, high emotionality and low sociability, skin reaction at the injection site and joint pain.] In total, one RCT and two prospective cohort studies provided evidence relating to adverse events at up to 12 months or 15 months follow-up for children with beta thalassaemia and iron overload. The RCT compared children who received either combination therapy with DFP/DFX or combination therapy with DFO/DFP. In the two prospective cohort studies patients received combination therapy with DFP/DFX or monotherapy with either DFP or DFX. **At 15 months:** • One prospective cohort study (Jhinger et al 2018) reported the number of different adverse events at 15 months follow-up with combination therapy with DFP/DFX (n=19) and monotherapy with DFP (n=10) or DFX (n=6). However, the number of children experiencing any adverse events in each group was not reported. The most common adverse events with DFP/DFX were transient proteinuria (53%), mild abdominal symptoms (16%) and mild neutropenia (16%). The most common adverse events with DFX monotherapy were transient proteinuria (67%), abdominal pain (50%) and rash (50%). The authors reported that no "significant" adverse events were observed with DFP monotherapy. **(VERY LOW)** **At 12 months:** • One RCT (Elalfy et al 2015) reported one serious adverse event in children receiving combination therapy with DFP/DFX (n=48) and one serious adverse event in children receiving combination therapy with DFO/DFP (n=48). No statistical comparison between groups reported.

Outcome	Evidence statement
	The serious adverse event for DFP/DFX was acute cholecystitis. It is not stated if this was considered drug-related. The serious adverse event for DFO/DFP was appendicitis which was not considered to be drug-related. **(MODERATE)** • The RCT also reported that the number of drug-related adverse events was 28 in 48 children (58.3%) receiving combination therapy with DFP/DFX and 26 in 48 children (54.2%) receiving combination therapy with DFO/DFP. No statistical comparison between groups reported. The drug-related adverse events were described as mostly of mild to moderate severity with the most common drug-related adverse events being neutropenia, arthralgia and gastrointestinal problems. **(MODERATE)** • The RCT also reported that the number of non-drug-related adverse events was 17 in 48 children (35.4%) receiving combination therapy with DFP/DFX and 18 in 48 children (37.5%) receiving combination therapy with DFO/DFP. No statistical comparison between groups reported. The most commonly reported non-drug-related adverse event was infection. **(MODERATE)** • One prospective cohort study (Gomber et al 2016) reported one adverse event (arthropathy of large joints) in 15 children (6.7%) receiving combination therapy with DFP/DFX and two adverse events (mild abdominal pain) in 17 children (11.8%) receiving monotherapy with DFX. No adverse events were reported for 17 children receiving monotherapy with DFP. No statistical comparison between groups reported. **(VERY LOW)** **One RCT reported moderate certainty evidence of one serious adverse event each for DFP/DFX and DFO/DFP combination therapies. The number of drug-related adverse events was 58% and 54% and the number of non-drug-related adverse events was 35% and 38% for DFP/DFX and DFO/DFP respectively. One prospective cohort study reported adverse events of 7% for combination therapy with DFP/DFX and 0% and 12% for monotherapy with DFP or DFX respectively. A second cohort study stated that the most common adverse events with DFP/DFX were transient proteinuria (53%), mild abdominal symptoms (16%) and mild neutropenia (16%) and that the most common adverse events with DFX monotherapy were transient proteinuria (67%), abdominal pain (50%) and rash (50%). The authors reported that no "significant" adverse events were observed with DFP monotherapy. No statistical comparison between groups was reported by any of the studies.**
Abbreviations ALT: Alanine transaminase; CI: Confidence intervals; dL: Decilitre; df: Degrees of freedom; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; g: Grams; Hb: Haemoglobin; kg: Kilogram; LVEF: Left ventricular ejection fraction; L: Litre; mg: Milligram; ml: Millilitres; ms: Milliseconds; MRI: Magnetic resonance imaging; ng: Nanograms; RCT: Randomised controlled trial; SD: Standard deviation; SF: short-form; SGPT: Serum glutamic-pyruvic transaminase; µg: Microgram	

In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the cost effectiveness of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from the combination of DFP and DFX more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients that would benefit from the combination of DFP/DFX more than the wider population of interest.**

From the evidence selected, what are the criteria used by the research studies to define those patients diagnosed with iron overload in chronic inherited anaemias who are eligible to commence treatment with the combination of DFP and DFX?

Outcome	Evidence statement
Criteria for treatment commencement with DFP/DFX	The inclusion criteria for the included studies were: In their RCT, Elalfy et al (2015) included children aged 10 to 18 years with severe iron overload, defined as serum ferritin >2500 µg/L on maximum tolerated dose of a single iron chelator with upwards trend of serum ferritin over the 12 months prior to the study. Patients with labile cellular iron >7 mg/g by MRI R2* and mean cardiac T2* <20 and >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, arrythmias). Adequacy of prior chelation was defined as taking >75% of the calculated dose/month on maximum tolerated dose with upward ferritin trend. For DXF this was reported to be 40 mg/kg/day, for DFP 100 mg/kg/day, for DFO >40-50 mg/kg. In their prospective cohort study, Gomber et al (2016) included children with serum ferritin >1500 ng/mL who were multi-transfused (not further defined). In their prospective study, Jhinger et al (2018) included children with serum ferritin >4000 ng/mL.
Abbreviations DFX: Deferasirox; DFP: Deferiprone; kg: Kilogram; L: Litre; mg: Milligram; ml: Millilitres; ms: Milliseconds; MRI: Magnetic resonance imaging; ng: Nanograms; RCT: Randomised controlled trial; µg: Microgram	

From the evidence selected, what dose of DFP and DFX was used?

Outcome	Evidence statement
Dose of DFP/DFX	In Elalfy et al (2015), the dose was DFP 75 mg/kg/day divided into two oral doses combined with a single oral dose of DFX 30 mg/kg/day orally. In Gomber et al (2016), the dose was DFP 75 mg/kg/day divided into three oral doses combined with DFX 30 mg/kg/day orally as a single dose. In Jhinger et al (2018), patients received DFP and DFX on alternate weeks. The DFP dose was 75-100 mg/kg/day monotherapy divided into three to four oral doses. The DFX dose was 30-40 mg/kg/day monotherapy as a single oral dose.
Abbreviations DFX: Deferasirox; DFP: Deferiprone; kg: Kilogram; mg: Milligram	

6. Discussion

This evidence review considered the clinical effectiveness and safety of DFP/DFX combination therapy for the treatment of iron overload in patients with chronic inherited anaemias. The critical outcomes of interest were quality of life, progression of iron overload and disease response. Important outcomes were adherence to treatment, psychological outcomes, mortality, activities of daily living and adverse events. Evidence on cost effectiveness was also sought.

Evidence was available from one RCT (Elalfy et al 2015) and two prospective cohort studies (Gomber et al 2016, Jhinger et al 2018). The RCT compared combination therapy with DFP/DFX to combination therapy with DFO/DFP. The two prospective cohort studies included patients receiving combination therapy with DFP/DFX or monotherapy with either DFP or DFX.

The RCT was conducted at two centres in Egypt and Oman. The prospective cohort studies were both conducted at single centres in India. The precise location in India was only stated for one of the studies. However, the affiliations of the authors suggests that the studies were conducted at two different centres. There is nothing to indicate that there was any overlap in the patients included in the two studies. It is not clear how generalisable these might be to other settings.

No studies were identified comparing the combination of DFP/DFX to DFO monotherapy or to no chelation therapy.

No evidence was identified for psychological outcomes or activities of daily living, both important outcomes, or for cost effectiveness.

The populations of all three included studies were children with beta thalassaemia. The further description or inclusion criteria for the populations of the three studies varied and applied to all groups of patients receiving the different treatments specified in the studies. In the RCT (Elalfy et al 2015) the children were described as having severe iron overload which was defined as serum ferritin >2500 µg/L on maximum tolerated dose of a single iron chelator with upwards trend of serum ferritin over the 12 months prior to the study. In the prospective cohort study by Gomber et al (2016), the children had a serum ferritin level of more than 1500 ng/mL and had received multiple transfusions. This was not further defined. In the prospective cohort study by Jhinger et al (2018), the children had a serum ferritin level of >4000 ng/mL. No other inclusion criteria were specified in this study.

Most of the patients in the included studies were receiving monotherapy prior to the start of the study. In the RCT by Elalfy et al (2015) there was a two-week washout period during which previous treatment was stopped prior to starting the study treatment, while the two prospective cohort studies had no washout period. The process of selecting patients to receive combination therapy was not clear in either of the prospective cohort studies. The dosing regimen for DFP/DFX also varied between the included studies. In the RCT by Elalfy et al (2015) and the prospective study by Gomber et al (2016) patients received 75 mg/kg/day of DFP in divided doses combined with a single dose of 30 mg/kg/day of DFX. In the prospective cohort study by Jhinger et al (2018) patients received DFP (75-100 mg/kg/day) and DFX (30-40 mg/kg/day) each for a week on alternate weeks.

The RCT included 96 children, 48 in each treatment group. The study authors had calculated that at least 47 pairs of patients would be needed to demonstrate a significant difference in mean serum ferritin between baseline and follow-up. The prospective cohort studies included 49 and 40 children respectively divided between the three treatment groups. However, in Gomber et al (2016) only 15 of the 49 patients were assessed for outcomes involving MRI scans (liver and cardiac iron). The authors stated that this was due

to financial constraints. It is not clear if the patients who received MRI assessment were similar to the patients who were not assessed.

The RCT and one of the prospective cohort studies (Gomber et al 2016) followed-up patients for 12 months. However, in Gomber et al (2016) some outcomes were only reported up to six months which may be too short a period to assess benefit. The other prospective cohort study (Jhinger et al 2018) followed patients up for 15 months. Patients and clinicians were not blinded to treatment group. This would not have been practical in the RCT due to the different delivery methods (DFP and DFX delivered orally and DFO by subcutaneous infusion). The lack of blinding may introduce potential bias to the self-reported outcome reported in the RCT. However, bias due to the lack of blinding is unlikely for the objective outcomes reported in the RCT and in the prospective cohort studies.

The included studies reported outcomes for DFP/DFX in comparison to three current standard therapies; combination therapy with DFO/DFP and monotherapy with DFP or DFX. All studies also assessed whether outcomes had improved compared to baseline for each of the chelation therapies assessed. The RCT reported findings for children receiving combination therapy with DFP/DFX compared to combination therapy with DFO/DFP for the critical outcomes of quality of life, progression of iron overload and disease response. These showed that there was no statistically significant difference in quality of life, improvement in serum ferritin or improvement in liver iron concentration (measured by MRI R2*) between combination therapy with DFP/DFX and combination therapy with DFO/DFP at 12 months with the quality of life and progression of iron overload outcomes showing a statistically significant improvement from baseline in both combination therapy groups. However, although cardiac iron (measured by MRI T2*) also improved from baseline to 12 months in both combination therapy groups, the improvement was statistically significantly greater for combination therapy with DFP/DFX than it was for combination therapy with DFP/DFO. For the critical outcome of disease response there was reported to be no difference in change from baseline to 12 months for mean left ventricular ejection fraction between DFP/DFX and DFO/DFP combination therapies, although no data or p values were reported.

The prospective cohort studies reported the critical outcome of progression of iron overload. In one prospective cohort study (Gomber et al 2016) there was a statistically significantly greater improvement from baseline to 12 months in serum ferritin level in children receiving combination therapy with DFP/DFX compared to monotherapy with either DFP or DFX. For the other elements of progression of iron overload (liver iron and cardiac iron, both measured by MRI T2*) there was no statistically significant difference in the change from baseline to six months for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. No statistical comparison between groups was reported for liver iron or cardiac iron.

The other prospective cohort study (Jhinger et al 2018) reported a statistically significant improvement in serum ferritin from baseline to 15 months for both combination therapy with DFP/DFX and monotherapy with DFP or DFX. There was no statistically significant difference between baseline and 15 months for liver iron or cardiac iron (both measured by MRI T2*) for either combination therapy with DFP/DFX or monotherapy with DFP or DFX. This study did not report a statistical comparison between combination therapy and monotherapy for progression of iron overload.

No data on combination therapy with DFP/DFX compared to monotherapy with DFP or DFX was identified for the critical outcomes of quality of life and disease response.

The RCT reported findings for children receiving combination therapy with DFP/DFX compared to combination therapy with DFO/DFP for the important outcomes of adherence to treatment and mortality. The RCT showed a statistically significantly greater adherence to treatment at 12 months follow-up for combination therapy with DFP/DFX than for combination therapy with DFO/DFP. In the prospective cohort study by Jhinger et al (2018) two out of 21 patients receiving combination therapy with DFP/DFX were excluded from the study due to poor compliance. No monotherapy patients were reported to be non-compliant with treatment. This study did not report a statistical comparison between combination therapy and monotherapy for this outcome. The RCT and one of the prospective studies (Gomber et al 2016) reported that no patients died during the 12-month follow-up period.

None of the studies commented on what minimal clinically important thresholds or differences would be for any of the outcomes considered.

All three included studies reported adverse events. However, none of the studies reported statistical comparison between the treatment groups. In the RCT, there was one serious adverse event each for DFP/DFX and DFO/DFP combination therapies. For DFP/DFX and DFO/DFP combination therapies respectively there were 58% and 54% drug-related adverse events and 35% and 38% non-drug-related adverse events. One prospective cohort study (Gomber et al 2016) reported adverse events of 7% for combination therapy with DFP/DFX and 0% and 12% for monotherapy with DFP or DFX respectively. The other prospective cohort study (Jhinger et al 2018) described the most common adverse events but did not report the number of children experiencing any adverse events in each treatment group.

The certainty in the outcomes reported by the RCT was high or moderate. Where issues were identified that could affect confidence in these results these related to the lack of patient blinding in relation to self-reported outcomes such as quality of life and lack of statistical analysis for some outcomes. In addition, there was a lack of detail in the reporting of some outcomes. For quality of life the baseline figures were provided, but quality of life scores at follow-up were only presented graphically. For cardiac function (disease response) a statement was made about the status of patients and the lack of difference between groups, but no absolute figures or p value were provided. Therefore, although appropriate analysis may have been performed in relation to the study's aims, the level of detail provided in the reporting was not always sufficient to fully understand or interpret the clinical significance of the results. For some outcomes the study authors could have reported summary statistics such as mean difference with confidence intervals for comparisons between treatment groups but did not provide these data. This meant that a judgement of the precision of these results could not be made in the GRADE assessment of these outcomes.

The certainty in the outcomes reported by the prospective cohort studies was very low. Factors that reduced confidence in the outcomes of both prospective cohort studies included lack of detail about the study populations, for example, limited details about baseline demographics and characteristics and whether the groups were similar at baseline. There was also no identification of or adjustment for potentially confounding variables, such as any other interventions received. The assessment of only a small number of the patients included in the study for some outcomes was another limitation for the study by Gomber et al (2016). The lack of statistical analysis was a limitation for some outcomes. In addition, the prospective cohort study by Jhinger et al (2018) could have but did not report any statistical comparisons between the treatment groups.

Consideration of the consistency of results between the included studies is difficult due to differences in the comparisons made and the way in which the outcomes were reported. No

studies reported any subgroup analysis about patients who might benefit more from treatment with DFP/DFX for the outcomes of interest.

7. Conclusion

This review included one RCT comparing combination therapy with DFP/DFX to combination therapy with DFO/DFP and two prospective cohort studies of combination therapy with DFP/DFX or monotherapy with DFP or DFX. The populations of all three studies were children with beta thalassaemia. No studies were identified comparing the combination of DFP/DFX to DFO monotherapy or to no chelation therapy.

One RCT provided high to moderate certainty evidence of no statistically significant difference between combination therapy with DFP/DFX and combination therapy with DFO/DFP at 12 months follow-up for the critical outcomes of quality of life, progression of iron overload (improvement in serum ferritin and improvement in liver iron concentration) and disease response, with the quality of life and progression or iron overload outcomes showing a statistically significant improvement from baseline in both combination therapy groups. For one element of the critical outcome of progression of iron overload (cardiac iron) and the important outcome of adherence to treatment, the results favoured combination therapy with DFP/DFX (high to moderate certainty). No patients died in either of the treatment groups. The number of serious adverse events, drug-related adverse events and non-drug-related adverse events appeared similar between the combination therapy groups, however no statistical comparison was reported (moderate certainty).

One prospective cohort study provided very low certainty evidence favouring combination therapy with DFP/DFX compared to monotherapy with DFP or DFX for the critical outcome of progression of iron overload (improvement in serum ferritin) with 12 months follow-up. There was no statistically significant difference between baseline and six months follow-up for combination therapy or monotherapy for other elements of the critical outcome of progression of iron overload (liver iron or cardiac iron). A second prospective cohort study reported an improvement in serum ferritin but no statistically significant difference for liver iron or cardiac iron from baseline to 15 months for both combination therapy with DFP/DFX and monotherapy with either DFP or DFX (very low certainty). This study did not report a statistical comparison between combination therapy and monotherapy for these outcomes. The number of patients who were non-compliant with treatment was reported by one prospective cohort study, however the treatment groups were not compared statistically. One prospective cohort study reported that no patients died in any of the treatment groups. Adverse events were reported for both prospective cohort studies but were not compared between groups (all very low certainty).

There was no evidence on activities of daily living, psychological outcomes or cost effectiveness or on any subgroups of patients who might benefit more from treatment.

Limitations reducing the certainty in the RCT outcomes included lack of patient blinding in relation to self-reported outcomes and lack of statistical analysis for some outcomes. Limitations reducing certainty in both the prospective cohort studies included lack of detail about the study populations and whether the groups were similar at baseline, lack of identification of or adjustment for potentially confounding variables and, for some outcomes, the inclusion of a limited number of the patients and lack of statistical analysis.

The studies identified for this review therefore provide high to moderate certainty evidence that overall, for children with beta thalassaemia there may little difference in effectiveness and safety for combination therapy with DFP/DFX and combination therapy with DFO/DFP, with better adherence to treatment with DFP/DFX. There was limited, very low certainty evidence that combination therapy with DFP/DFX may have better outcomes than DFP or DFX monotherapy in terms of improvement in serum ferritin levels from baseline. The

limitations of the studies comparing combination therapy with DFP/DFX to monotherapy limit the conclusions that can be drawn for this comparison.

Appendix A PICO Document

The review questions for this evidence review are:

1. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the clinical effectiveness of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

2. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the safety of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

3. In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the cost effectiveness of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

4. From the evidence selected, are there any subgroups of patients that may benefit from the combination of DFP and DFX more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those patients diagnosed with iron overload in chronic inherited anaemias who are eligible to commence treatment with the combination of DFP and DFX?

6. From the evidence selected, what dose of DFP and DFX was used?

P-Population and Indication	Adults and children diagnosed with chronic inherited anaemias who develop iron overload (sometimes called haemosiderosis). Patients can either be transfused or non-transfused. [Inherited anaemia is an umbrella term covering a number of haemoglobinopathies and other red cell disorders passed down in families. They include sickle cell disease, thalassaemia, and other rare anaemias including Diamond Blackfan anaemia (DBA), sideroblastic anaemia (SA), pyruvate kinase deficiency (PKD), G6PD deficiency and rare red cell membrane disorders, congenital dyserythropoietic anaemias and enzymopathies].
I-Intervention	DFP and DFX combination therapy at any stage of the treatment pathway
C-Comparator	Current standard treatments, which are: 1.DFO monotherapy 2.DFP monotherapy 3.DFX monotherapy 4.DFO/DFP combination Or No chelation therapy
O-Outcomes	**<u>Clinical Effectiveness</u>** There are no known standard MCIDs for any of the outcomes measured. Outcomes measures at 1 year or more are of particular interest. **Critical to decision making** • **Quality of life**

	This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms. • **Progression of iron overload** Preventing complications of disease and its progression is important to patients as it has the potential to maintain engagement in activities of daily living and prevent increasing dependence on others. Progression, or lack of progression, of iron deposition in tissues can provide critical information on treatment effectiveness. Iron burden in the liver reflects total body iron and iron in the heart is associated with increased mortality. Changes in iron stores can be determined sooner than overall survival outcome measures and therefore a useful survival outcome for trials with shorter follow-up periods. [Examples of measures include: liver iron stores as measured by R2MRI or T2* cardiac or liver iron assessment or persistently raised ferritin in those unable to undergo an MRI assessment. • **Disease response** (including but not limited to improvement in cardiac function, endocrine function (including pituitary, pancreatic, reproductive and bone health), reduction of hepatic iron stores or other validated measures of organ function). This outcome is important to patients because it can reflect the benefits the treatment may have for a patient. This can be important to control the symptomatic burden of the disease and/or reflect subgroups who may configure additional response benefits, allowing the treatment protocol to be individualised. **Important to decision making** • **Adherence to treatment** This is important to patients because it is vital to the function of iron chelating drugs that they are taken regularly as prescribed in order to gain the maximum effect, improve iron burden and prevent the complications of iron overload. • **Psychological outcomes** These outcomes are important to patients because they can impact their mood, motivation and self esteem which can have implications for treatment compliance. Positive healthcare outcomes rely upon patients' ability to comply with their rigorous treatment regimes. Delayed puberty due to poor iron control is the most common endocrine complication in thalassaemia. Often this can result in diminished self-esteem and body confidence as the secondary conditions causes illnesses that can deform, debilitate and disable them. Lack of concordance can be a ubiquitous threat to not only patients' physical health but compound their psychosocial well-being. • **Mortality** Mortality is usually the gold standard for assessing survival benefit of drug treatments. This outcome is important to patients because it considers whether the treatment reduces

	mortality although it does not reflect morbidity or patient experience. • **Activities of daily living (ADLs)** ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home and recreational settings. They encompass patients' individual rehabilitation goals and facilitate inclusion and participation. **<u>Adverse Events</u>** • Adverse events are important to patients because they will impact on their treatment choices, adherence, recovery and could have long term sequelae if they are irreversible. It reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the additional demands placed on the health system to manage the adverse consequences of the treatment. • [Serious adverse events include agranulocytosis, renal impairment, heart failure, and severe gastrointestinal side effects (e.g. perforated gastric ulcer). Common adverse effects include gastrointestinal disturbances (such as dyspepsia, gastrointestinal pain, nausea, vomiting, diarrhoea, and constipation), somatic complaints, physical symptoms, high emotionality and low sociability, skin reaction at the injection site and joint pain.] **Cost effectiveness** • Studies of the cost effectiveness of iron chelation therapy reporting for example, cost per QALY, ICERs, incremental QALYs, incremental cost per patient or time to reach a cost effectiveness threshold.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2011-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase, and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. PubMed was also used to identify similar articles linked from key clinical papers. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

One search was performed to identify studies on DFP/DFX, the subject of this evidence review, and studies on DFO/DFX which is considered in a separate evidence review.

Search dates: 1 January 2011 to 1 July 2021

Medline search strategy:

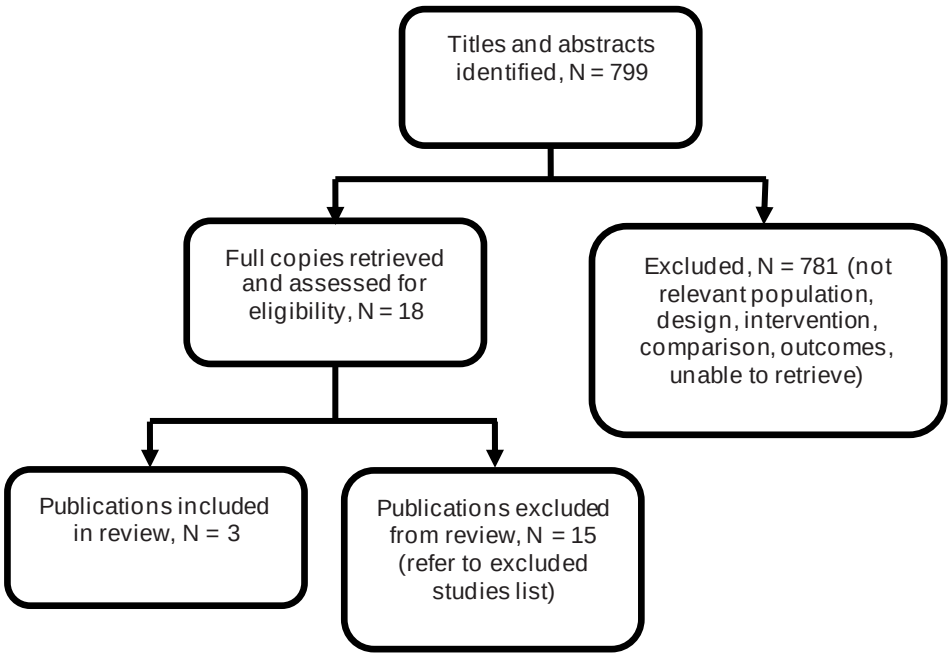
1	Deferasirox/ and Deferiprone/
2	Deferoxamine/ and Deferasirox/
3	((deferasirox or exjade) and (deferiprone or ferriprox)).ti,ab,kw.
4	((Deferasirox or exjade) and (deferoxamine or deferoximine or desferroxamine or desferroximine or desferal)).ti,ab,kw.
5	1 or 2 or 3 or 4
6	Deferasirox/
7	Deferiprone/
8	Deferoxamine/
9	Iron Chelating Agents/
10	Chelation Therapy/
11	(Deferasirox or exjade or deferoxamine or deferoximine or desferroxamine or desferroximine or desferal or deferiprone or ferriprox).ti,ab,kw.
12	(((chelation or chelating) adj2 (therap* or treatment? or drug? or agent?)) or (iron adj2 chelator?)).ti,ab,kw.
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	Drug Combinations/
15	Drug Therapy, Combination/
16	(combin* adj3 (therap* or treatment*)).ti,ab,kw. or combin*.ti.
17	14 or 15 or 16
18	13 and 17
19	5 or 18
20	exp anemia, hypoplastic, congenital/ or exp anemia, hemolytic/ or anemia, sideroblastic/ or exp red-cell aplasia, pure/
21	(thalass?mia? or ((congenital or sickle cell or black fan or blackfan or sideroblastic or chronic or inherited or inborn) adj3 an?emia?) or (h?emoglobinopath* or enzymopath* or pyruvate kinase deficien* or g6pd deficien* or red cell aplasia? or (red cell adj2 disorder?))).ti,ab,kw.
22	*Iron Overload/
23	(iron overload or h?emosidorosis).ti.
24	20 or 21 or 22 or 23
25	19 and 24

26	limit 25 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
27	(comment or editorial or letter or review).pt. or case report.ti.
28	25 not 27
29	exp animals/ not humans/
30	28 not 29
31	26 or 30
32	limit 31 to (english language and yr="2011 -Current")

Appendix C Evidence selection

The combined literature search identified 799 potential references. These were screened using their titles and abstracts and 18 references potentially relating to a combination of DFP/DFX were obtained in full text and assessed for relevance. Of these, three references are included in this evidence review. The 15 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Elalfy MS, Adly AM, Wali Y, Tony S, Samir A, Elhenawy YI. Efficacy and safety of a novel combination of two oral chelators deferasirox (DFX)/deferiprone (DFP) over deferoxamine (DFO)/deferiprone (DFP) in severely iron overloaded young beta thalassemia major patients. Eur J Haematol. 2015 Nov;95(5):411-20.	Included in the review
Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone (DFP) and deferasirox (DFX) combination is efficacious in iron overloaded patients with B-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015 Sep;62(9):1592-6.	Excluded. Non-comparative study. Comparative studies available for the outcomes reported
Lin CH, Chen X, Wu CC, Wu KH, Song TS, Weng TF, Hsieh YW, Peng CT. Therapeutic mechanism of combined oral chelation therapy to maximize efficacy of iron removal in transfusion-dependent thalassemia major - a pilot study. Expert Rev Hematol. 2019 Apr;12(4):265-272.	Excluded. Does not report any outcomes listed in the PICO

Appendix D Excluded studies table

Study reference	Reason for exclusion
Bollig C, Schell LK, Rucker G, Allert R, Motschall E, Niemeyer CM, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database of Systematic Reviews. 2017;8:CD007476.	No pooled analysis for DFP/DFX combination. Individual studies considered separately
Bordbar M, Haghpanah S, Zekavat OR, Saki F, Bazrafshan A, Bozorgi H. Effect of different iron chelation regimens on bone mass in transfusion-dependent thalassemia patients. Expert Review of Hematology. 2019;12(11):997-1003.	No patients received a combination of DFP/DFX
Botzenhardt S, Li N, Chan EW, Sing CW, Wong IC, Neubert A. Safety profiles of iron chelators in young patients with haemoglobinopathies. European Journal of Haematology. 2017;98(3):198-217.	Review only used data from the intervention arm of comparative studies. Comparative analysis has been included from the individual studies
DivakarJose RR, Delhikumar CG, Ram Kumar G. Efficacy and safety of combined oral chelation with deferiprone and deferasirox on iron overload in transfusion dependent children with thalassemia - A prospective observational study. Indian Journal of Pediatrics. 2021;88(4):330-5.	Non-comparative study. Comparative studies available for the outcomes reported
Farmaki K, Tzoumari I, Pappa C. Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells, Molecules and Diseases. 2011;47:33-40.	Non-comparative study. Comparative studies available for the outcomes reported
Karami H, Kosaryan M, Amree AH, Darvishi-Khezri H, Mousavi M. Combination iron chelation therapy with deferiprone and deferasirox in iron-overloaded patients with transfusion-dependent beta-thalassemia major. Clinica Practica. 2017;7(1):912.	Non-comparative study. Comparative studies available for the outcomes reported
Kwiatkowski JL, Kim HY, Thompson AA, Quinn CT, Mueller BU, Odame I, et al. Chelation use and iron burden in North American and British thalassemia patients: a report from the Thalassemia Longitudinal Cohort. Blood. 2012;119(12):2746-53.	No patients received a combination of DFP/DFX
Lin CH, Chen X, Wu CC, Wu KH, Song TS, Weng TF, et al. Therapeutic mechanism of combined oral chelation therapy to maximize efficacy of iron removal in transfusion-dependent thalassemia major - a pilot study. Expert Rev Hematol. 2019;12(4):265-72.	Does not report any outcomes listed in the PICO
Maaloul I, Laaroussi O, Jedidi I, Sfaihi L, Kmiha S, Kamoun T, et al. Management of patients with major beta thalassemia in a paediatric department in the south of Tunisia: About 26 cases. Transfusion Clinique et Biologique. 2018;25(1):14-8.	Full text not available in English
Olivieri NF, Sabouhanian A, Gallie BL. Single-center retrospective study of the effectiveness and toxicity of the oral iron chelating drugs deferiprone and deferasirox. PLoS ONE [Electronic Resource]. 2019;14(2):e0211942.	Non-comparative study. Comparative studies available for the outcomes reported
Parakh N, Chandra J, Sharma S, Dhingra B, Jain R, Mahto D. Efficacy and safety of combined oral chelation with deferiprone and deferasirox in children with β-thalassemia major: An experience from North India. J Pediatr Hematol Oncol. 2017;39(3):209-13.	Non-comparative study. Comparative studies available for the outcomes reported
Santra S, Bhattacharya A, Mukhopadhyay T, Agrawal D, Kumar S, Das P, et al. Use of iron chelating agents in transfusion dependent thalassaemia major patients. Mymensingh Medical Journal: MMJ. 2015;24(4):838-44.	Does not report any outcomes listed in the PICO
Song TS, Hsieh YW, Peng CT, Chen TL, Lee HZ, Chung JG, et al. Combined versus monotherapy or concurrent therapy for treatment of thalassaemia. In Vivo. 2014;28(4):645-9.	Does not report any outcomes listed in the PICO
Sridharan K, Sivaramakrishnan G. Efficacy and safety of iron chelators in thalassemia and sickle cell disease: a multiple treatment comparison network meta-analysis and trial sequential analysis. Expert Rev Clin Pharmacol. 2018;11(6):641-50.	No patients received a combination of DFP/DFX

Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with β-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015;62(9):1592-6.	Non-comparative study. Comparative studies available for the outcomes reported

Appendix E Evidence Table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Elalfy MS, Adly AM, Wali Y, Tony S, Samir A, Elhenawy YI. Efficacy and safety of a novel combination of two oral chelators deferasirox/ deferiprone over deferoxamine/ deferiprone in severely iron overloaded young beta thalassemia major patients. Eur J Haematol. 2015;95(5):411-20. **Study location** 2 treatment centres in Egypt and Oman **Study type** RCT **Study aim** To compare the safety, efficacy, compliance, treatment satisfaction and quality of life of 2 combination chelation regimens	Children with β-thalassaemia and severe iron overload **Inclusion criteria** Age 10 to 18 years. Severe iron overload, defined as serum ferritin >2500 µg/L on maximum tolerated dose of a single iron chelator with upwards trend of serum ferritin over the 12 months prior to the study. Patients with labile cellular iron >7 mg/g by MRI R2* and mean cardiac T2* <20 and >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, arrythmias). Adequacy of prior	**Intervention** DFP 75 mg/kg/day divided into 2 doses orally at 8am and 3pm combined with DFX 30 mg/kg/day orally at 10pm **Comparison** DFO 40 mg/kg/day by subcutaneous infusion over 10 hours starting at 10pm for 6 days per week combined with DFP 75 mg/kg/day divided into 2 doses orally at 8am and 3pm for 7 days per week **Concomitant treatments** The transfusion regimen aimed to maintain the patients pretransfusion haemoglobin ≥8 g/dL. Patients received approximately 15 ml/kg packed red	Patients followed-up monthly for 12 months **Critical outcomes** **Quality of life** Assessed using the SF-36[11] mean ± SD No statistically significant difference in quality of life between groups at 12 months (p=0.860) DFP/DFX (n=48) • Baseline: 63.38 ± 5.98 • 12 months: Data reported graphically but figure not reported Statistically significant improvement from baseline to 12 months, p=0.02 DFO/DFP (n=48) • Baseline: 63.09 ± 5.77 • 12 months: Data reported graphically but figure not reported Statistically significant improvement from baseline to 12 months, p=0.01	This study was appraised using the JBI checklist for RCTs: 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments** This was an open-label RCT and it would not have been practical to blind patients or clinicians to the treatment groups due to the differences in delivery methods. It is possible that the lack of blinding may introduce a potential bias for self-reported measures. However, it is unlikely to impact the objective outcomes reported. The lack of blinding for the clinicians delivering

[11] The SF-36 is scored from 0 to 100 with higher scores indicating better quality of life

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates Study dates not stated	chelation was defined as taking >75% of the calculated dose/month on maximum tolerated dose with upward ferritin trend. For DFX this should be 40 mg/kg/day, for DFP 100 mg/kg/day, for DFO >40-50 mg/kg **Exclusion criteria** Past history of agranulocytosis, clinically significant gastrointestinal or renal disease, clinical cardiac disease or left ventricular ejection fraction <50% on baseline echocardiography. Evidence of active hepatitis or serum transaminases >3 times above upper limit of normal or renal impairment (serum creatinine > upper limit of normal). Participation in a previous investigational drug	blood cells every 3-4 weeks Patients consumed a low iron diet (1-15mg of iron per day) throughout the study	**Progression of iron overload** ***Serum ferritin levels µg/L*** Multiple regression analysis against time showed no statistically significant difference in improvement from baseline between groups[12]. Regression coefficients (elevation and slope) ± standard error: • DFP/DFX 4212.85 ± 119.17 - 89.1 ± 15.38t • DFO/DFP 4383.98 ± 114.92 - 62.78 ± 14.84t Comparison of elevation and slope (d.f.=286), p=0.301 and 0.218 respectively DFP/DFX mean ± SD (n=48) • Baseline: 4289.19 ± 866.21 • 6 months: 3525.57 ± 952.31 (percent change -17.8%) • 12 months: 3219.98 ± 882.25 (percent change -36.59%) Significantly better at 12 months compared to 6 months and baseline, p=0.001 DFO/DFP mean ± SD (n=48) • Baseline: 4379.07 ± 895.00 • 6 months: 4017.15 ± 861.33 (percent change -8.26%) • 12 months: 3625.76 ± 869.13 (percent change -17.2%) Significantly better at 12 months compared to 6 months and baseline, p=0.001	treatment is unlikely to bias the outcomes reported in this study. The data management and data analysis were blinded to treatment group. The two groups were similar at baseline except for a statistically significant difference in baseline haemoglobin. The groups were described as comparable with regards to baseline clinical, quality of life and haematological parameters by the study authors. The sample size was based on a power calculation that concluded that at least 47 pairs of patients would be needed to demonstrate a significant difference in mean serum ferritin between baseline and follow-up. Patients were receiving iron chelation therapy prior to the study. This was discontinued for a 2-week washout period before randomisation. The authors stated that no patients were lost to follow-up. All patients were included in the analyses reported.

[12] The linear regression analysis assessed the changes in each variable against time with calculation of the difference between the slopes (elevation and slope) of the studied groups. A significant difference between the slopes indicates that the therapy has produced significantly different effects between groups

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	study within 30 days preceding screening. Known allergy to DFX, DFP and DFO **Total sample size** n=96 DFP/DFX: n=48 DFO/DFP: n=48 **Baseline characteristics** *DFP/DFX* Male: 66.6% Age years (mean ± SD): 14.05 ± 2.21 *DFO/DFP* Male: 62.5% Age years (mean ± SD): 15.25 ± 2.31 Groups were similar at baseline for age, sex, percentage of patients with excellent/good levels of compliance to chelation therapy, baseline clinical quality of life and haematological parameters, baseline iron burden, ALT and serum creatine, absolute neutrophil		***Liver iron concentration by MRI R2* mg/g*** Multiple regression analysis against time showed no statistically significant difference in improvement from baseline between groups. Regression coefficients (elevation and slope) ± standard error: • DFP/DFX 12.823 ± 0.286 – 0.196 ± 0.037t • DFO/DFP 12.732 ± 0.285 – 0.146 ± 0.037t Comparison of elevation and slope (d.f.=286), p=0.340 and 0.821 respectively DFP/DFX mean ± SD (n=48) • Baseline: 12.52 ± 2.28 • 6 months: 12.25 ± 1.9 (percent change -2.15%) • 12 months: 10.17 ± 2.23 (percent change -18.77%) Significantly better at 12 months compared to 6 months and baseline, p=0.001 DFO/DFP mean ± SD (n=48) • Baseline: 12.69 ± 2.23 • 6 months: 11.95 ± 1.01 (percent change -5.8%) • 12 months: 10.96 ± 2.95 (percent change -13.6%) Significantly better at 12 months compared to 6 months and baseline, p=0.001	The outcomes assessed were either objective clinical measures or self-reported using validated questionnaires and the statistical analysis used overall was appropriate. However, for some outcomes the detail of the analysis was not adequately reported in the paper. For quality of life the baseline figures were provided, but quality of life scores at follow-up were only presented graphically. For some questions relating to adherence to treatment, a statement and p value was reported but no numerical detail of the result. For cardiac function a statement was made about the status of patients and the lack of difference between groups, but no absolute figures or p value were provided. For some outcomes the study authors could have reported summary statistics such as mean difference with confidence intervals for comparisons between treatment groups but did not provide these data. The study was conducted in 2 centres in Egypt and Oman and the study years were not stated.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	count and quality of life There was a statistically significant difference between groups in baseline haemoglobin (DFP/DFX 7.90 ± 0.38 Hb/g/dL vs DFO/DFP 8.11 ± 0.33 Hb/g/dL) Chelation therapy was withdrawn for 2 weeks before randomisation as a washout period Mean age at first transfusion: 8.5 months (range 5-15)		***Cardiac iron overload by MRI T2* ms*** Multiple regression analysis against time showed that cardiac T2* improved significantly more from baseline for DFP/DFX than DFO/DFP. Regression coefficients (elevation and slope) ± standard error: • DFP/DFX 16.656 ± 0.254 – 0.263 ± 0.033t • DFO/DFP 16.352 ± 0.210 – 0.125 ± 0.027t Comparison of elevation and slope (d.f.=286), p=0.357 and 0.001 respectively DFP/DFX geometric mean[13] ± SD (n=48) • Baseline: 16.59 ± 1.85 • 6 months: 18.36 ± 0.86 (percent change +10.67%) • 12 months: 19.75 ± 2.65 (percent change +19.1%) Significantly better at 12 months compared to 6 months and baseline, p=0.001 DFO/DFP geometric mean ± SD (n=48) • Baseline: 16.32 ± 1.82 • 6 months: 17.17 ± 0.87 (percent change +5.21%) • 12 months: 17.8 ± 1.89 (percent change +9.1%) Significantly better at 12 months compared to 6 months and baseline, p=0.002	The generalisability of the results to the NHS in England is unclear. **Source of funding:** No statement on source of funding. The authors stated that they had no conflicts of interest to declare.

[13] Geometric means calculated from the log-transformed T2* values

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Disease response The authors reported no difference in change from baseline in mean LVEF at 12 months between DFP/DFX and DFO/DFP. Data and p value not reported The authors reported that mean LVEF remained stable and within the normal range after 12 months in both groups[14]. No patients in either group had impaired ejection fraction or deterioration in cardiac function by echocardiography during follow-up **Important outcomes** **Adherence to treatment** Treatment compliance[15] (12 months) • DFP/DFX (n=48): 95% • DFO/DFP (n=48): 80% p<0.001 The authors stated that the proportion of patients who reported always following their iron chelation therapy was statistically significantly higher for DFP/DFX compared to DFO/DFP (p<0.001). Data not reported The authors stated that the proportion of patients who never thought about stopping iron chelation therapy was statistically significantly	

[14] Impaired left ventricular function was defined by a decrease in resting LVEF either to a value <50% or by >10% units between 2 consecutive measurements. Patients with suspected cardiac manifestations had chest radiography, electrocardiogram and echocardiography
[15] Patients' compliance was evaluated by counting the returned tablets for DFP and DFX and of the vials for DFO. The percentage of actual dose that patient had taken in relation to the total dose prescribed was calculated

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			higher for DFP/DFX compared to DFO/DFP (p<0.02). Data not reported **Mortality** The authors stated that no patients died during the study **Safety** ***Serious adverse events*** No serious adverse events required discontinuation or interruption of therapy in either group One DFP/DFX patient experienced a serious adverse event (acute cholecystitis). It is not stated if this was considered drug-related One DFO/DFP patient experienced a non-drug related serious adverse event (appendicitis) ***Adverse events*** *Drug-related adverse events* • DFP/DFX (n=48): 28 (58.3%) These were described as being of mild to moderate severity • Neutropenia: 5 (10.4%) • Arthralgia: 8 (16.6%) • Gastrointestinal problems: 6 (12.5%) • ALT (increase ≥3 fold): 4 (8.3%) • Serum creatine (≥33%) above baseline on 2 consecutive occasions: 3 (6.3%) • Skin rash: 2 (4.2%) • DFO/DFP (n=48): 26 (54.2%)	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			These were described as being mostly of mild to moderate severity • Neutropenia: 3 (6.3%) • Arthralgia: 9 (18.7%) • Gastrointestinal problems: 10 (20.8%) • ALT (increase ≥3 folds): 3 (6.3%) • Serum creatine (≥33%) above baseline on 2 consecutive occasions: 1 (2.1%) In addition, 5 DFP/DFX and 3 DFO/DFP patients had mild elevation of hepatic transaminases at the start of therapy that returned to normal within 2 months with no interference *Non-drug-related adverse events* • DFP/DFX (n=48): 17 (35.4%) • Infections: 12 (25%) • Gastrointestinal disorders: 3 (6.3%) • Skin and subcutaneous tissue disorders: 2 (4.2%) • DFO/DFP (n=48): 18 (37.5%) • Infections: 11 (22.9%) • Gastrointestinal disorders: 3 (6.3%) • Skin and subcutaneous tissue disorders: 4 (8.3%)	
Gomber S, Jain P, Sharma S, Narang M. Comparative Efficacy and Safety of Oral Iron Chelators and their Novel Combination in Children with Thalassemia. Indian	Children with beta thalassaemia who had received multiple transfusions **Inclusion criteria** Serum ferritin >1500 ng/mL. Multi-	**Intervention** DFP 75 mg/kg/day divided into 3 oral doses combined with DFX 30 mg/kg/day orally as a single dose **Comparison**	Patients were assessed at baseline, 6 months and 12 months **Critical outcomes** **Progression of iron overload** ***Serum ferritin levels ng/mL mean (95%CI)***	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. No

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Pediatr. 2016;53(3):207-10. **Study location** 1 centre in India **Study type** Prospective cohort study **Study aim** To compare the efficacy and safety of DFP and DFX used singly and in combination **Study dates** Study dates not stated	transfused (not further defined) **Exclusion criteria** History of anaphylaxis due to DFP or DFX; serum creatinine value above the upper limit of normal for that age **Total sample size** n=49 DFP/DFX: n=15 DFP: n=17 DFX: n=17 **Baseline characteristics** Male: 61.2% Age years (mean; SD): 11.6; 6.21 Groups were similar at baseline for serum ferritin values	DFP 75 mg/kg/day monotherapy divided into 3 oral doses DFX 30 mg/kg/day monotherapy as a single dose **Concomitant treatments** Patients received packed red blood cell transfusion very 3 weeks to maintain a pre-transfusion haemoglobin level of 9 to 9.5 g/dL	DFP/DFX (n=15) • Baseline: 3696.5 (3079.6 to 4438.1) • 6 months: 2977.1 (2384.5 to 3717.1) • 12 months: 2572.1 (2138.9 to 3093.1) DFP (n=17) • Baseline: 3140.5 (2617.5 to 3767.9) • 6 months: 3010.9 (2548.5 to 3557.1) • 12 months: 2910.0 (2220.7 to 3812.4) DFX (n=17) • Baseline: 3859.2 (3168.8 to 4700.0) • 6 months: 3671.1 (3098.1 to 4350.1) • 12 months: 3417.4 (2734.6 to 4270.7) For the decrease (improvement) in serum ferritin levels: • DFP/DFX vs DFP: p=0.035 • DFP/DFX vs DFX: p=0.04 The authors reported that the monotherapy drugs had similar efficacy ***Liver MRI T2* ms mean (SD)*** DFP/DFX (n=5) • Baseline: 5.3 (0.26) • 6 months: 5.5 (0.40) DFP (n=5) • Baseline: 5.4 (0.20) • 6 months: 5.6 (0.26) DFX (n=5)	5. No 6. No 7. Yes 8. Yes 9. No 10. No 11. Yes **Other comments**: In this prospective, uncontrolled cohort study 44 of the 49 patients were receiving chelation with DFP or DFX monotherapy prior to this study. The remaining 5 were new patients who had not previously received iron chelation therapy. No washout period was reported between previous treatments and the treatment specified in this study. There was limited information or comparison of the groups at baseline. The authors used a computer-generated random number table to select 6 children from those already receiving DFP or DFX monotherapy to receive combination therapy. The remaining 3 patients in the combined therapy group had not previously received chelation therapy. It is not clear how these

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Baseline: 5.1 (0.52) • 6 months: 5.4 (0.58) The authors reported that liver iron load was higher (meaning a reduced iron load on liver) in all 3 groups, but that there was no statistically significant reduction in any of the groups (p not reported). The iron overload range at baseline (5.1 to 5.4) and 6 months (5.4 to 5.6) was categorised as mild by the authors[16] ***Heart MRI T2* ms mean (SD)*** DFP/DFX (n=5) • Baseline: 29.5 (1.99) • 6 months: 31.2 (2.57) DFP (n=5) • Baseline: 33.3 (1.44) • 6 months: 32.3 (1.66) DFX (n=5) • Baseline: 32.0 (2.00) • 6 months: 31.7 (2.65) The authors stated that the mean values were "almost similar" at baseline (29.5 to 33.3ms) and 6 months (31.2 to 32.3) with the difference being "insignificant" (p not reported). These figures for heart iron overload were categorised as none by the authors[17]	children were selected to receive combination therapy. Most outcomes were reported up to 12 months follow-up. However, some outcomes were only reported up to 6 months. Statistical analysis was not reported for all outcomes. The follow-up of patients was complete for the study overall. However, not all of the included patients were included in the analysis of all outcomes. MRI was only done for 5 patients in each group, less than a third of the total patients. The authors stated that this was due to financial constraints. It is not clear if the patients who received MRI assessment were similar to the patients who were not assessed. It would not have been practical to blind patients or clinicians to the treatment groups due to the differences in delivery methods. The outcomes assessed were objective clinical measures.

[16] Liver iron overload was graded as none >6.3ms; mild 6.3 to 2.7ms; moderate 2.7 to 1.4ms; severe <1.4ms
[17] Heart iron overload was graded as none >20ms; mild 12-20ms; moderate 8-12ms; severe <8ms

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Important outcomes **Mortality** The authors stated that no patients died during the study **Safety** DFP/DFX (n=15) • Arthropathy of large joints within 4 weeks which subsided after discontinuation of DFP (n=1, 6.7%) DFP (n=17) • No adverse effects observed DFX (n=17) • Mild abdominal pain which subsided with 7-10 days oral proton pump inhibitors. No discontinuation of treatment required (n=2, 11.8%) The authors stated that no patients developed neutropaenia, thrombocytopaenia or derangements of kidney function tests	The study was conducted in 1 centre in India and the study years were not stated. The generalisability of the results to the NHS in England is unclear. **Source of funding:** Funding was received from Thalassaemia India
Jhinger P, Sobti PC, Kaushal S, Kakkar S. Combination of two oral iron chelators in patients with thalassemia major. Pediatric Hematology Oncology Journal. 2018;3(3):55-8.	Children with beta thalassaemia **Inclusion criteria** Serum ferritin >4000 ng/mL. **Exclusion criteria**	**Intervention** DFP and DFX received on alternate weeks. DFP 75-100 mg/kg/day monotherapy divided into 3-4 oral doses. DFX 30-40 mg/kg/day	Patients were followed up for 15 months. 35 patients completed the study protocol **Critical outcomes** **Progression of iron overload** ***Serum ferritin levels ng/mL mean (SD)***	This study was appraised using the JBI checklist for cohort studies: 1. Unclear 2. Yes 3. Yes 4. No 5. No

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study location 1 centre in India **Study type** Prospective cohort study **Study aim** To assess the efficacy of a DFP and DFX sequential regimen **Study dates** Study dates not stated	Lack of compliance (intake of <75% of prescribed doses), known toxicity or intolerance to any of the oral iron chelators, neutropaenia (neutrophil <1.0 x 10^9/L), thrombocytopaenia (platelet <100 x 10^9/L), presence of renal or hepatic disease **Total sample size** n=40 DFP/DFX: n=21 DFP: n=10 DFX: n=9 **Baseline characteristics** Male: 65.71% Age years (mean; SD): 9.71; 3.38 No statistical comparison of the groups at baseline was reported	monotherapy as a single oral dose **Comparison** DFP 75-100 mg/kg/day monotherapy divided into 3-4 oral doses DFX 30-40 mg/kg/day monotherapy as a single dose **Concomitant treatments** No information was provided about any concomitant treatments	DFP/DFX (n=19) • Baseline: 4763.17 (1022) • 15 months: 4023.56 (1084) p=0.029 DFP (n=10) • Baseline: 5574.13 (1497) • 15 months: 3388.88 (755) p=0.011 DFX (n=6) • Baseline: 4394.5 (666) • 15 months: 2988.83 (820) p=0.004 ***Liver MRI T2* ms mean (SD)*** DFP/DFX (n=19) • Baseline: 5.62 (0.99) • 15 months: 5.69 (0.87) p=0.806 DFP (n=10) • Baseline: 6.19 (1.97) • 15 months: 5.55 (0.44) p=0.260 DFX (n=6) • Baseline: 5.89 (0.70) • 15 months: 5.55 (0.65) p=0.119	6. No 7. Yes 8. Yes 9. No 10. No 11. No **Other comments**: In this prospective, uncontrolled cohort study little information was provided about the patients at baseline. Patients were receiving monotherapy with either DFP or DFX prior to the study. No washout period was reported between previous treatments and the treatment specified in this study. The study authors describe the patients as being randomised to the 3 study groups however no details are provided and one patient opted to receive combination therapy rather than monotherapy with DFX. The study was not described as a RCT by the authors. Although groups of patients received different treatments, no statistical comparison between treatment groups was reported. Five of the 40 patients who initially met the inclusion criteria

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			These figures for liver iron overload were categorised as mild by the authors[18] ***Cardiac MRI T2* ms mean (SD)*** DFP/DFX (n=19) • Baseline: 29.82 (3.28) • 15 months: 28.03 (3.23) p=0.51 DFP (n=10) • Baseline: 28.67 (4.56) • 15 months: 30.72 (4.38) p=0.07 DFX (n=6) • Baseline: 29.97 (4.01) • 15 months: 29.75 (4.66) p=0.901 These figures for heart iron overload were categorised as none by the authors[19] **Important outcomes** **Adherence to treatment** 2/21 DFP/DFX patients were excluded from the study due to poor compliance **Safety** DFP/DFX (n=19) • Transient proteinuria (n=10, 52.6%)	were excluded from the study. Two DFP/DFX patients and 3 DFX patients. The 3 DFX patients were excluded from the analysis due to very high serum ferritin levels within 6 months of the start of the study which required DFO transfusion. The 2 DFP/DFX patients were excluded from the study due to poor compliance. It would not have been practical to blind patients or clinicians to the treatment groups due to the differences in delivery methods. The outcomes assessed were objective clinical measures. The study was conducted in 1 centre in India and the study years were not stated. The generalisability of the results to the NHS in England is unclear. **Source of funding:** No statement on source of funding or conflicts of interest

[18] Liver iron overload was graded as none >6.3ms; mild 6.3 to 2.7ms; moderate 2.7 to 1.4ms; severe <1.4ms
[19] Heart iron overload was graded as none >20ms; mild 12-20ms; moderate 8-12ms; severe <8ms

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Mild abdominal symptoms (n=3, 16%) • Mild neutropaenia which required transient cessation of combination treatment for a week (n=3, 16%) • Rash (n=1, 5%) • Arthralgia (n=1, 5%) • Elevated SGPT at 2 times upper limit requiring DFX dose decrease (n=1, 5%) The authors stated that no serious adverse events were observed DFP (n=10) • No “significant” adverse effects observed DFX (n=6) The most common adverse events were: • Transient proteinuria (n=4, 66.67%) • Abdominal pain (n=3, 50%) • Rash (n=3, 50%) • Deranged SGPT at 4 times the upper limit which normalised after dose reduction (n=1, 17%) The authors stated that no worsening of serum creatine was observed in any group	

Abbreviations
ALT: Alanine transaminase; CI: Confidence intervals; dL: Decilitre; df: Degrees of freedom; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; g: Grams; Hb: Haemoglobin; kg: Kilogram; LVEF: Left ventricular ejection fraction; L: Litre; mg: Milligram; ml: Millilitres; ms: Milliseconds; MRI: Magnetic resonance imaging; ng: Nanograms; RCT: Randomised controlled trial; SD: Standard deviation; SF: short-form; SGPT: Serum glutamic-pyruvic transaminase; µg: Microgram

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blinded to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisations, parallel groups) accounted for in the conduct and analysis of the trial

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

In patients diagnosed with chronic inherited anaemias who develop iron overload, what is the clinical effectiveness and safety of the combination of DFP and DFX compared to current standard treatment or no chelation therapy?

For abbreviations and footnotes see end of tables.

Table 2. Combination therapy with DFP and DFX compared to combination therapy with DFO and DFP

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	DFP/DFX	DFO/DFP	Result		
Quality of life (1 RCT)									
Quality of life at 12 months assessed by SF-36 mean ± SD (benefit indicated by higher score)									
1 RCT Elalfy et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	48	48	No statistically significant difference between groups at 12 months (p=0.860) Baseline • DFP/DFX: 63.38 ± 5.98 • DFO/DFP: 63.09 ± 5.77 Data at 12 months only reported graphically DFP/DFX baseline to 12 months p=0.02 DFO/DFP baseline to 12 months p=0.01	Critical	Moderate
Progression of iron overload (1 RCT)									
Serum ferritin levels µg/L. Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error). 12-month follow-up (benefit indicated by a lower score)									
1 RCT Elalfy et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	48	48	No statistically significant difference in decrease from baseline between groups • DFP/DFX 4212.85 ± 119.17 - 89.1 ± 15.38t	Critical	High

							• DFO/DFP 4383.98 ± 114.92 - 62.78 ± 14.84t Comparison of elevation and slope (d.f.=286), p=0.301 and 0.218 respectively DFP/DFX (mean ± SD): • Baseline: 4289.19 ± 866.21 • 6 months: 3525.57 ± 952.31 (percent change -17.8%) • 12 months: 3219.98 ± 882.25 (percent change -36.59%) 12 months compared to 6 months and baseline p=0.001 DFO/DFP mean ± SD: • Baseline: 4379.07 ± 895.00 • 6 months: 4017.15 ± 861.33 (percent change -8.26%) • 12 months: 3625.76 ± 869.13 (percent change -17.2%) 12 months compared to 6 months and baseline p=0.001		
Liver iron concentration by MRI R2* mg/g. Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error). 12-month follow-up (benefit indicated by a lower score)									
1 RCT Elalfy et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	48	48	No statistically significant difference in decrease from baseline between groups • DFP/DFX 12.823 ± 0.286 – 0.196 ± 0.037t • DFO/DFP 12.732 ± 0.285 – 0.146 ± 0.037t Comparison of elevation and slope (d.f.=286), p=0.340 and 0.821 respectively	Critical	High

							DFP/DFX mean ± SD: • Baseline: 12.52 ± 2.28 • 6 months: 12.25 ± 1.9 (percent change -2.15%) • 12 months: 10.17 ± 2.23 (percent change -18.77%) 12 months compared to 6 months and baseline p=0.001 DFO/DFP mean ± SD: • Baseline: 12.69 ± 2.23 • 6 months: 11.95 ± 1.01 (percent change -5.8%) • 12 months: 10.96 ± 2.95 (percent change -13.6%) 12 months compared to 6 months and baseline p=0.001		
Cardiac MRI T2* ms. Multiple regression analysis against time (regression coefficients (elevation and slope) ± standard error). 12-month follow-up (benefit indicated by a higher score)									
1 RCT Elalfy et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	48	48	Statistically significant improvement for DFP/DFX vs DFO/DFP • DFP/DFX 16.656 ± 0.254 – 0.263 ± 0.033t • DFO/DFP 16.352 ± 0.210 – 0.125 ± 0.027t Comparison of elevation and slope (d.f.=286), p=0.357 and 0.001 respectively DFP/DFX geometric mean ± SD: • Baseline: 16.59 ± 1.85 • 6 months: 18.36 ± 0.86 (percent change +10.67%) • 12 months: 19.75 ± 2.65 (percent change +19.1%) 12 months compared to 6 months and baseline p=0.001 DFO/DFP geometric mean ± SD: • Baseline: 16.32 ± 1.82	Critical	High

							• 6 months: 17.17 ± 0.87 (percent change +5.21%) • 12 months: 17.8 ± 1.89 (percent change +9.1%) 12 months compared to 6 months and baseline p=0.002		
Disease response (1 RCT)									
LVEF change from baseline to 12 months									
1 RCT Elalfy et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	48	48	Authors reported "no difference" between the 2 groups. Data and p value not reported Mean LVEF remained stable and within the normal range after 12 months in both groups	Critical	Moderate
Adherence to treatment (1 RCT)									
Percentage of patients compliant with treatment. 12 months follow-up (benefit indicated by a higher score)									
1 RCT Elalfy et al 2015	No serious limitations	No serious indirectness	Not applicable	Not calculable	48	48	• DFP/DFX: 95% • DFO/DFP: 80% p<0.001	Important	High
Proportion of patients who reported always following their iron chelation therapy. 12 months follow-up (benefit indicated by a higher score)									
1 RCT Elalfy et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	48	48	The authors stated that the proportion of patients who reported always following their iron chelation therapy was statistically significantly higher for DFP/DFX compared to DFO/DFP (p<0.001). Data not reported	Important	Moderate
Proportion of patients who reported that they never thought about stopping iron chelation therapy. 12 months follow-up (benefit indicated by a higher score)									
1 RCT Elalfy et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	48	48	The authors stated that the proportion of patients who never thought about stopping iron chelation therapy was statistically significantly higher for DFP/DFX compared to DFO/DFP (p<0.02). Data not reported	Important	Moderate

Mortality (1 RCT)									
Number of deaths at 12 months follow-up									
1 RCT Elalfy et al 2015	No serious limitations	No serious indirectness	Not applicable	Serious imprecision[3]	0/48 (0%)	0/48 (0%)	No patients died during the 12 months follow-up	Important	Moderate
Safety (1 RCT)									
Number of serious adverse events. 12 months follow-up									
1 RCT Elalfy et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	1/48 (2.1%)	1/48 (2.1%)	No statistical comparison between groups reported	Important	Moderate
Number of drug-related adverse events. 12 months follow-up									
1 RCT Elalfy et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	28/48 (58.3%)	26/48 (54.2%)	No statistical comparison between groups reported	Important	Moderate
Number of non-drug-related adverse events. 12 months follow-up									
1 RCT Elalfy et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	17/48 (35.4%)	18/48 (37.5%)	No statistical comparison between groups reported	Important	Moderate

Abbreviations
df: Degrees of freedom; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; g: Grams; LVEF: Left ventricular ejection fraction; L: Litre; mg: Milligram; ms: Milliseconds; MRI: Magnetic resonance imaging; RCT: Randomised controlled trial; SD: Standard deviation; SF: short-form; µg: Microgram

1. Risk of bias. Serious limitations due to lack of patient blinding for this self-reported outcome
2. Risk of bias. Serious limitations due to lack of statistical analysis
3. Imprecision: Serious imprecision due to 0 events in both arms

Table 3. Combination therapy with DFP/DFX compared to monotherapy with DFP or DFX

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	DFP/DFX	Monotherapy	Result		
Progression of iron overload (2 cohort studies)									
Serum ferritin levels from baseline to 12 months ng/mL mean (95%CI) (benefit indicated by a lower score)									
1 prospective cohort study Gomber et al 2016	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	15	DFP: 17	Greater decrease for DFP/DFX vs DFP: p=0.035 DFP/DFX: • Baseline: 3696.5 (3079.6 to 4438.1) • 6 months: 2977.1 (2384.5 to 3717.1) • 12 months: 2572.1 (2138.9 to 3093.1) DFP: • Baseline: 3140.5 (2617.5 to 3767.9) • 6 months: 3010.9 (2548.5 to 3557.1) • 12 months: 2910.0 (2220.7 to 3812.4)	Critical	Very low
1 prospective cohort study Gomber et al 2016	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	15	DFX: 17	Greater decrease for DFP/DFX vs DFP: p=0.04 DFP/DFX: • Baseline: 3696.5 (3079.6 to 4438.1) • 6 months: 2977.1 (2384.5 to 3717.1) • 12 months: 2572.1 (2138.9 to 3093.1) DFX: • Baseline: 3859.2 (3168.8 to 4700.0)	Critical	Very low

							• 6 months: 3671.1 (3098.1 to 4350.1) • 12 months: 3417.4 (2734.6 to 4270.7)		
Serum ferritin levels from baseline to 15 months ng/mL mean (SD) (benefit indicated by a lower score)									
1 prospective cohort study Jhinger et al 2018	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	19	DFP: 10 DFX: 6	No statistical comparison between groups reported DFP/DFX: • Baseline: 4763.17 (1022) • 15 months: 4023.56 (1084) p=0.029 DFP: • Baseline: 5574.13 (1497) • 15 months: 3388.88 (755) p=0.011 DFX: • Baseline: 4394.5 (666) • 15 months: 2988.83 (820) p=0.004	Critical	Very low
Liver MRI T2* from baseline to 6 months ms mean (SD) (benefit indicated by a higher score)									
1 prospective cohort study Gomber et al 2016	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	5	DFP: 5 DFX: 5	No statistical comparison between groups reported DFP/DFX: • Baseline: 5.3 (0.26) • 6 months: 5.5 (0.40) The authors reported no statistically significant difference (p not reported) DFP: • Baseline: 5.4 (0.20) • 6 months: 5.6 (0.26) The authors reported no statistically significant difference (p not reported)	Critical	Very low

							DFX: • Baseline: 5.1 (0.52) • 6 months: 5.4 (0.58) The authors reported no statistically significant difference (p not reported)		
Liver MRI T2* from baseline to 15 months ms mean (SD) (benefit indicated by a higher score)									
1 prospective cohort study Jhinger et al 2018	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	19	DFP: 10 DFX: 6	No statistical comparison between groups reported DFP/DFX: • Baseline: 5.62 (0.99) • 15 months: 5.69 (0.87) p=0.806 DFP: • Baseline: 6.19 (1.97) • 15 months: 5.55 (0.44) p=0.260 DFX: • Baseline: 5.89 (0.70) • 15 months: 5.55 (0.65) p=0.119	Critical	Very low
Heart MRI T2* from baseline to 6 months ms mean (SD) (benefit indicated by a higher score)									
1 prospective cohort study Gomber et al 2016	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	5	DFP: 5 DFX: 5	No statistical comparison between groups reported DFP/DFX: • Baseline: 29.5 (1.99) • 6 months: 31.2 (2.57) DFP: • Baseline: 33.3 (1.44) • 6 months: 32.3 (1.66) DFX: • Baseline: 32.0 (2.00) • 6 months: 31.7 (2.65)	Critical	Very low

							The authors stated that the mean values were “almost similar” at baseline and 6 months with the difference being “insignificant” (p not reported)		
Cardiac MRI T2* from baseline to 15 months ms mean (SD) (benefit indicated by a higher score)									
1 prospective cohort study Jhinger et al 2018	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	19	DFP: 10 DFX: 6	No statistical comparison between groups reported DFP/DFX: • Baseline: 29.82 (3.28) • 15 months: 28.03 (3.23) p=0.51 DFP: • Baseline: 28.67 (4.56) • 15 months: 30.72 (4.38) p=0.07 DFX: • Baseline: 29.97 (4.01) • 15 months: 29.75 (4.66) p=0.901	Critical	Very low
Adherence to treatment									
Number non-compliant with treatment. 15 months follow-up									
1 prospective cohort study Jhinger et al 2018	Very serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[4]	2/21 (9.5%)	DFP: 0/10 (0%) DFX: 0/6 (0%)	No statistical comparison between groups reported	Important	Very low
Mortality (1 prospective cohort study)									
Number of deaths at 12 months follow-up									
1 prospective cohort study	Very serious limitations[1]	No serious indirectness	Not applicable	Serious imprecision[5]	0/15 (0%)	DFP: 0/17 (0%) DFX: 0/17 (0%)	No patients died during the 12 months follow-up	Important	Very low

Gomber et al 2016									
Safety (2 prospective cohort studies)									
Number of adverse events at 12 months follow-up									
1 prospective cohort study Gomber et al 2016	Very serious limitations[2]	No serious indirectness	Not applicable	Serious imprecision[4]	1/15 (6.7%)	DFP: 0/17 (0%) DFX: 2/17 (11.8%)	No statistical comparison between groups reported	Important	Very low
Adverse events at 15 months follow-up									
1 prospective cohort study Jhinger et al 2018	Very serious limitations[2]	No serious indirectness	Not applicable	Not calculable	19	DFP: 10 DFX: 6	No statistical comparison between groups reported DFP/DFX • Transient proteinuria (n=10, 52.6%) • Mild abdominal symptoms (n=3, 16%) • Mild neutropaenia which required transient cessation of combination treatment for a week (n=3, 16%) • Rash (n=1, 5%) • Arthralgia (n=1, 5%) • Elevated SGPT at 2 times the upper limit for which DFX dose was decreased (n=1, 5%) No serious adverse events were observed DFP • No “significant” adverse effects observed	Important	Very low

							DFX The most common adverse events were: • Transient proteinuria (n=4, 66.67%) • Abdominal pain (n=3, 50%) • Rash (n=3, 50%) • Deranged SGPT at 4 times the upper limit which normalised after dose reduction (n=1, 17%)		

Abbreviations
CI: Confidence intervals; DFX: Deferasirox; DFP: Deferiprone; DFO: Desferrioxamine; ml: Millilitres; ms: Milliseconds; MRI: Magnetic resonance imaging; ng: Nanograms; SD: Standard deviation; SGPT: Serum glutamic-pyruvic transaminase

1. Risk of bias. Very serious limitations due to lack of detail about the study population, lack of clarity about the similarity between the groups at baseline and lack of identification of and adjustment for potential confounding factors
2. Risk of bias. Very serious limitations due to lack of detail about the study population, lack of clarity about the similarity between the groups at baseline, lack of identification of and adjustment for potential confounding factors and lack of statistical analysis between groups
3. Risk of bias. Very serious limitations due to lack of detail about the study population, lack of clarity about the similarity between the groups at baseline, lack of identification of and adjustment for potential confounding factors, lack of inclusion of all patients and lack of statistical analysis between groups
4. Imprecision: Serious imprecision due to 0 events in a comparator arm
5. Imprecision: Serious imprecision due to 0 events in both arms

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the

	other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Elalfy MS, Adly AM, Wali Y, Tony S, Samir A, Elhenawy YI. Efficacy and safety of a novel combination of two oral chelators deferasirox/ deferiprone over deferoxamine/ deferiprone in severely iron overloaded young beta thalassemia major patients. Eur J Haematol. 2015;95(5):411-20.
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